

**PROTECTING HUMAN SUBJECTS IN RESEARCH:
ARE CURRENT SAFEGUARDS ADEQUATE?**

HEARING
BEFORE THE
SUBCOMMITTEE ON PUBLIC HEALTH
OF THE
COMMITTEE ON HEALTH, EDUCATION,
LABOR, AND PENSIONS
UNITED STATES SENATE
ONE HUNDRED SEVENTH CONGRESS
SECOND SESSION
ON

EXAMINING CURRENT SAFEGUARDS CONCERNING THE PROTECTION OF HUMAN
SUBJECTS IN RESEARCH, WHILE FACILITATING CRITICAL MEDICAL RESEARCH

APRIL 23, 2002

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PROTECTING HUMAN SUBJECTS IN RE- SEARCH: ARE CURRENT SAFEGUARDS ADE- QUATE?

TUESDAY, APRIL 23, 2002

U.S. SENATE,
SUBCOMMITTEE ON PUBLIC HEALTH, OF THE COMMITTEE ON
HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 10:02 a.m., in room SD-430, Dirksen Senate Office Building, Hon. Edward M. Kennedy [chairman of the committee] presiding.

Present: Chairman Kennedy; Senators Murray, and Frist.

OPENING STATEMENT OF SENATOR EDWARD KENNEDY

The CHAIRMAN. The hearing will come to order.

Senator Frist will be here in a moment or two.

We have a vote scheduled at around 11 o'clock which is going to temporarily interrupt the hearing, and then it will resume, so we want to apologize in advance to our witnesses for the interruption, but that is something which we had no control over.

Today's hearing is on the important issue of protecting patients who volunteer as subjects in clinical trials and other forms of research. Numerous expert reports and investigations on our current system of protections have identified serious flaws that must be corrected, and I look forward to working with Senator Frist and other members of our committee on legislation that will improve the current system.

The task is urgent. Transplants, chemotherapy, and countless medications that we now take for granted today were once experimental and unproven. These medical miracles are available to patients today only because they were tested on people who participated in clinical research studies.

None of us knows what new medical breakthroughs are just around the corner. We can be sure, however, that any new cure or treatment will first be tested on human subjects. If patients fear that their safety is not adequately protected in medical research, these cures of the future will be placed in jeopardy. Patients will suffer if we do not protect those who volunteer to test newly discovered cures.

In an earlier hearing, our committee heard the harrowing testimony of Paul Gelsinger, whose son Jesse lost his life in a gene therapy clinical trial. Our investigation of Jesse's death revealed a

failure of our system of protections and allegations that financial conflicts of interest caused ethical lapses.

Today we will hear from Cherlynn Mathias, who had the courage to report to Federal investigators the abuses of human subject protection she witnessed at the University of Oklahoma. For this act of courage and integrity, she was harassed at work and forced to leave the job she loved. Congress must not ignore Paul Gelsinger's loss or Cherlynn Mathias' courage.

Today's hearing continues our committee's long interest in this issue. Nearly 30 years ago, we heard testimony that impoverished African Americans at the Tuskegee Institute had been used as guinea pigs in shameful medical experiments on syphilis. And we learned that an experimental birth control drug was tested on women at the Arlington School for the Mentally Retarded without their knowledge and without the consent of their legal guardians. We also know about the sterilization of the Relf girls, and we had hearings on the CIA, where they effectively provided toxic substances to some of the agents with the idea of developing antidotes, with a tragic outcome with regard to one particular family.

In response to these disturbing facts, our committee approved legislation that established basic protections for human subjects in federally-funded research. This oversight structure has served us well for a generation.

But the protections of the past are proving inadequate to keep up with the pace and volume of new discoveries. When the original legislation was enacted, clinical trials were conducted on a few dozen subjects at a single institution. Few researchers at universities had financial ties to drug companies, and "biotechnology" was not yet even a word, much less a national industry. But clinical research has changed significantly since then, and those changes have strained our system of research protections to the breaking point.

Today, newspapers carry stories about the crisis of confidence that is causing patients to refuse to participate in trials and imperils medical progress. Our responsibility is clear. We must revitalize our system of protections for this new century of the life sciences.

We must ensure that patients are properly informed about the research in which they participate. We should make certain that all patients who volunteer for clinical trials are protected by a strong and consistent set of safeguards, and we should prohibit improper financial conflicts of interest that can put patients at risk. We should ensure effective oversight of clinical trials by institutional review boards that meet high professional standards.

I look forward to the testimony of our witnesses and to working with our colleagues on this important issue.

I want to express my own appreciation to my colleague and friend, Senator Frist, for his work in this area and look forward to hearing from him now.

OPENING STATEMENT OF SENATOR BILL FRIST

Senator FRIST. Thank you, Mr. Chairman.

I want to thank you for rescheduling today's hearing to examine what I regard as one of the most critical but oftentimes overlooked issues facing America's research enterprises.

In the past few years, we have witnessed a true explosion particularly in the realms of biomedical and other scientific research which is very positive, which gives great hope and tremendous promise for people who either are suffering today from debilitating diseases or, as we look to tomorrow, offers great potential for prevention as well as response and treatment.

This movement is one in which Congress has been heavily invested in terms of dollars, in terms of resources—more than \$20 billion last year alone at the National Institutes of Health.

Last year, more than 2.3 million people completed clinical trials, and thousands more are currently participating in trials and other investigations. This is an important part of the investigative process in order to determine what is in the best interest of patients long-term.

The environment is producing medical breakthroughs, and it is one to which patients and families are looking for even more dramatic advances in our knowledge and ability to fight disease. As Senator Kennedy mentioned, recent tragedies have indeed shaken the public's trust and confidence.

Congress has made clear its commitment to biomedical research. Our research community and Federal research agencies have made clear their dedication to sound science and innovation. However, until recently, there has been too little attention focused on protecting the individuals who are at the heart of this critical research and who themselves make real personal sacrifices to make these miracles a reality.

Following the death of Jesse Gelsinger in 1999, we held two hearings to examine the oversight structures responsible for ensuring the safety of patients enrolled in gene therapy clinical trials. Through these hearings, it became clear that there had been a systemic breakdown of oversight, ranging from the investigators to the institutional review boards to the Federal agencies responsible for ensuring the safety of patients.

Since that time, I have been encouraged by a renewed focus among individual researchers, among research institutions and Federal agencies on improving the protections available to individuals participating in all forms of human subjects research.

In the past year since this hearing was scheduled, we have made great strides toward improving our system of protections and our underlying knowledge base. For instance, the Administration has put forward proposed modifications of the privacy rule that we will be discussing over the course of the morning. In addition, last year, two reports, including one that we commissioned by the General Accounting Office, helped shed new light on the issue of financial conflicts of interest.

However, there is much, much more that needs to be done. We are here today to examine these issues, to weigh and to evaluate the remaining gaps in our systems of oversight, and to consider the need for legislative action to improve protections for research subjects.

Mr. Chairman, I look forward to working with you as we develop this legislation and look forward to hearing from our witnesses today.

The CHAIRMAN. Very good. Thank you.

Senator Gregg has asked that a statement be included in the record, and without objection, that will be done.

I also have a prepared statement from Senator Jeffords to be included in the record.

[The prepared statement of Senator Gregg follows:]

PREPARED STATEMENT OF SENATOR JUDD GREGG

Clinical trials play a vital role in new product development. Clinical trials give patients access to the latest, most innovative cancer therapies, while helping researchers develop the next generation of treatments and medicines.

It is equally important, however, that we protect the rights and welfare of those who agree to participate in such research. Research must respect the autonomy of participants; be fair in both conception and implementation; maximize potential benefits; and minimize possible harms. Many view the current system of human subjects protections as inconsistent and inadequate. Some in Congress have called for legislation.

In order to both protect research participants and promote ethically responsible research, I believe that any legislation in this area must embody certain fundamental principals. Such legislation should:

- Centralize and streamline the Department of Health and Human Services' (HHS) oversight structures and regulations;
- Establish a single Federal office with authority over all HHS regulated or sponsored research;
- Establish safeguards for research participants that are strong, yet flexible enough to adapt to new, evolving research requirements;
- Ensure that the subject's participation was obtained through voluntary, informed consent;
- Encourage voluntary accreditation of Institutional Review Boards (IRBs) and investigators, and provide additional Federal resources for educating and training IRBs and investigators;
- Develop and distribute best practices;
- Improve and ensure oversight of Federal rules for disclosure, review and management of financial conflicts of interest; and
- Promote the effective and consistent enforcement of protections for participants in federally-sponsored or regulated research in the United States and abroad.

New safeguards should not unnecessarily burden and create disproportionate workload demands on HHS and researchers. In that regard, such legislation should be developed collaboratively with HHS, patient groups, investigators, research institutions, industry and other stakeholders. Our goal should be a balanced approach that protects research participants, promotes ethically responsible research, and ensures the continued development of next-generation treatments and medicines. I look forward to hearing from our witnesses and hear their views on how Congress and other stakeholders can best achieve this goal.

Thank you.

PREPARED STATEMENT OF SENATOR JAMES M. JEFFORDS

Mr. Chairman, I wish to thank you for holding this hearing on "Protecting Human Subjects in Research." This hearing continues the HELP Committee's examination of this issue that began during the last Congress, and you and Senator Frist are to be commended for your leadership. I would also like to extend a warm welcome to the panel of expert witnesses here today. I look forward to your testimonies so that we may all gain a better understanding of the current controversy surrounding the use of humans as subjects in clinical trials. This issue is crucial to improving the safety and health of all Americans.

Currently, the only universal standard for reviewing clinical research that involves human participants are institutional review boards (IRBs), that were created under the National Research Act of 1974. Under this act, IRBs are required to review, approve, and monitor all federally-funded research. However, in light of recent events regarding human subject testing, it has become clear that more must be done to protect participants in clinical research trials.

When I read Ms. Mathias' statement, I was astonished at her description of the Melanoma Clinical Trial. According to Ms. Mathias, many of the basic guidelines were never followed; and even more troublesome, many procedures in the study were not even reviewed, but instead appeared to have been created on the fly. Cases like this, where there were inappropriate decisions made with regard to the procedures of the study, and cases such as the University of Pennsylvania and the Johns Hopkins University clinical trials, in which subjects actually died, show us just how much we need to improve our current system of reviewing and monitoring trials.

Clinical trials are one of the best ways to develop new treatments and drugs, but they must follow proper procedure, or the safety of the participants and the legitimacy of the data will be in question. It is imperative for participants to be fully informed and for the administrators of the trial to fully follow their pre-approved procedures. The administrators must fully disclose all aspects of the trial, including funding and possible side-effects, and must run the trial in the most conscientious manner possible. Patients must be fully informed on all the stages of the trial as to all the possible side effects or complications that may arise from the treatment plan; they must know who is providing funding for the trial; and they must be fully informed on the entire procedure the doctor plans to follow. That same procedure must be implemented by the letter or the participants must be informed as to how and why it is being modified.

There have been many suggestions as to how to improve the clinical trial procedures for human subjects, and I am looking forward to hearing from our witnesses today. I agree with our panelist from the Association of American Medical Colleges, Mr. Kelch, when he says that accreditation is a good way to encourage self-review and evaluation while maintaining a high standard of review. The creation of the Association for the Accreditation of Human Research Protection Programs (AAHRPP) was truly an innovative idea that

deserves further examination as it may have a tremendous benefit on improving standards for clinical trials. Mr. Chairman, I understand that you are working on a measure that would require all IRB's to be accredited, an approach that I feel holds great promise. But, whatever our solution, it needs to speak first to the needs of the subjects to ensure their safety. I look forward to working with you on it.

It is of the utmost importance that we move quickly to protect human subjects in clinical trials. While clinical trials provide us with one of the best ways to develop treatments that save lives, they must also be conducted with safety as the number one priority. Thank you for organizing these important hearings today, and I am looking forward to learning more from our witnesses.

The CHAIRMAN. We have the privilege today of welcoming a distinguished panel of experts who will share their views on protecting human subjects in biomedical research. It often takes an act of courage to change a flawed system, and our first witness is such an example of courage.

It would have been easy for Cherlynn Mathias to turn a blind eye to the abuses of human subject protection she witnessed as clinical trials manager at the University of Oklahoma. But instead of taking the easy way out, Ms. Mathias had the courage to report these abuses, first to her university and ultimately to the Federal Office of Human Research Protection. For this act of courage, she was hounded out of work and forced to leave the job she loved.

Her integrity is an inspiration, and her testimony is an important reminder of the urgent need to revitalize research subject protections.

Dr. Marjorie Speers has devoted much of her career to human subject protection issues in medical research. She is executive director of the Association for the Accreditation of Human Research Protection Programs, whose purpose is to ensure high ethical standards for institutions conducting research. Previously, she was project director for the excellent report on human subject protection written by the National Bioethics Advisory Commission.

Congress is indebted to the fine reports of the Commission which reflected extraordinary contributions from many commissioners and the staff.

Dr. Charles Johnson is clinical research director at Genentech and will be testifying today on behalf of the Biotechnology Industry Organization. We look forward to his testimony on the view of biotechnology companies on human subject protection issues.

Dr. David Charles is chairman of the National Alliance of Medical Researchers and Teaching Physicians, an organization of physicians and scientists focused on improving medicine through technology. Dr. Charles also serves as director of the Movement Disorders Clinic at Vanderbilt University Medical Center. He has already contributed to our committee by working as a health policy fellow in Senator Frist's office a few years ago. We welcome him back to the committee today.

Cherlynn Mathias, we would be delighted to hear from you. We want to thank you for coming. We know it is not always easy, but your message is enormously important and very valuable, and it will make a difference in terms of trying to help people, which I

know you are very committed to. So we want you to relax and tell us your story, please.

STATEMENT OF CHERLYNN MATHIAS, MANAGER, CLINICAL RESEARCH DEPARTMENT, HARRIS METHODIST FORT WORTH HOSPITAL

Ms. MATHIAS. I am Cherlynn Mathias, a registered nurse currently working as manager of the Clinical Research Department at Harris Methodist Fort Worth. Today I am here to testify about my experiences as a study coordinator at the University of Oklahoma.

I was hired in June of 1999, and almost immediately, I realized that ineligible subjects were being enrolled into the melanoma clinical trial that Dr. J. Michael McGee was conducting. When I asked about the subjects being ineligible, I was told that McGee, as the principal investigator, could enroll whomever he wished and that the conduct of the study was his responsibility.

I found this perplexing, since I knew that the enrolled subjects were too old. And enrolling subjects who were still on other treatments and giving the drug to pregnant women were all violations of eligibility that FDA would also consider safety violations.

In late July, Dr. McGee requested that I build a database and gather statistics for publication. The building of a database required me to do a retrospective chart review of all melanoma vaccine patients. I discovered that several patients had been allowed to self-inject the vaccine. The patients who were self-injecting were storing the vaccine at home in their refrigerators. Not only was I alarmed by this finding, because of the obvious concern of drug accountability recordkeeping and storage of an experimental drug in an unsecured environment, but I was also concerned about patient safety.

The vaccine protocol called for the drug to be stored at the temperature of liquid nitrogen. I wondered if the vaccine was stable at higher temperatures. Also, the patients were at risk for drug reactions. It was obvious that adverse event monitoring was lacking.

In July, after discovering that the monitoring plan had never been developed, I was able to convince Dr. McGee to travel to another site in Springfield, Missouri. We discovered that the drug was being kept in the refrigerator-freezer which was located in the staff lounge. The drug was not in a secure location, and there was no temperature monitoring occurring at all.

Institutional review boards, IRBs, are the gatekeepers for the safety and welfare of the human subjects, as mandated by the Federal regulations. However, we found out that the oncologist had never sought local IRB approval, although he himself was an IRB member.

In October, I discovered that the current version of the protocol had never been submitted to the IRB, although it had been in use for 7 months. However, the Oklahoma University IRB had approved a change in the informed consent, which new title and contact information included St. John's Medical Center. This is significant, because the study was never submitted to the St. John's IRB even though the St. John's IRB chair was also a member of the Oklahoma University IRB, and he was present when the change was voted on.

I informed McGee that we were using an unapproved version of the protocol and informed consent. He was surprised and disbelieved the information. After a discussion, he agreed that I should contact the Oklahoma University IRB administrator.

The administrator met with Dr. McGee and me in late October, and he gave us some bad advice. He said that the IRB was not concerned about monitoring or study design issues. He also said that the problems concerning the other sites and their approval was none of the IRB's business, but rather an FDA matter. He instructed us to write protocol amendments that he would get approved to cover us retrospectively.

In November, retrospective amendments were submitted to the IRB. They included major changes to the study design. These changes included a plan to allow patients to self-inject, increase the size of the trial, addition of a second drug, GM-CSF, and other modifications to the protocol. These are but a few examples of where patients' safety and welfare were compromised as mandated by the Federal regulations.

I continued to be concerned about the trial. I had already started staying late at night and reading everything I could find on the FDA website concerning good clinical practices, good manufacturing practices, and good laboratory practices. The more I read, the more alarmed I became.

I started asking questions about manufacturing processes and became convinced that the lab was out of compliance as well. Many of the required safety testing for new lots of vaccine had never been completed. Plus the vaccine was not being manufactured in a sterile environment. In fact, when these vaccine preparations were tested on experimental animals, many of the animals either became sick, lost weight, or died.

The failure of the testing clearly presented a clear risk of infection to the patients. But McGee continued to increase enrollment.

Soon thereafter, I started following the chain of command within the medical college and sounding the alarm for what I saw as serious noncompliance with the Federal regulations that were put in place to protect human subjects. Eventually, this led me all the way to the top of the medical college. By the time I blew the whistle in June of 2000, the university had formed a committee that included the dean of the medical college, the director of the office of research, the IRB chair, the lab director, Dr. McGee, our department chair, and myself. The committee was engaged in acts of coverup instead of promptly reporting as required by the Federal regulations.

Since necessary actions were not being taken, I was compelled to report these violations to the Office of Human Research Protection. The oath that I took when I became a registered nurse was that I would be a patient advocate. I was haunted by the images, but in particular, one image continued to eat at me. It was the informed consent process. By now, I knew that it had been coercive to promise subjects that the melanoma vaccine offered hope for a cure.

Adverse event reporting was practically nonexistent. Unfortunately, the sad situation of not reporting adverse events is the

same across the Nation, as was found by a study conducted by the University of Maryland School of Medicine and Dr. Adil Shamoo.

Today, the university has adopted many positive changes in the way research is conducted. The president of Oklahoma University is David Boren. I believe in David Boren. In my opinion, he is one of Oklahoma's greatest assets. The university is in the process of implementing a model compliance program, and David Boren, the president of Oklahoma University, is committed to doing so. One of the changes he has put in place is greater protections for whistleblowers.

I am a graduate of Oklahoma University, and actually, in my own way, I love the university.

Thank you, honorable Senators, for inviting me to speak.

[The prepared statement of Ms. Mathias follows:]

PREPARED STATEMENT OF CHERLYNN MATHIAS

I am Cherlynn Mathias, a registered nurse currently working as the manager of the Clinical Research Department at Harris Methodist Fort Worth, a large community hospital in Texas. However, today I am here to testify about my experiences as a study coordinator at the University of Oklahoma.

I was hired in June of 1999, and almost immediately I realized that ineligible subjects were being enrolled into the melanoma clinical trial that J. Michael McGee was conducting. The trial had actually opened 3 years before my employment. When I asked about the subjects being ineligible, I was told that McGee, as the principal investigator, (clinical researcher), could enroll whomever he wished and that the conduct of the study was his responsibility.

In late July, Dr. McGee requested that I build a database, which contained endpoints not described in his study design. The purpose of the database was to gather statistics for publication and also for an upcoming medical conference in which McGee was scheduled to speak. The building of the database required me to do a retrospective chart review of all the melanoma vaccine patients. In the course of doing the chart reviews, I discovered that several patients had been allowed to self-inject the vaccine. The patients who were self-injecting were storing the vaccine at home in their refrigerators. Not only was I surprised by this finding, because of the obvious concern for drug accountability recordkeeping and storage of the experimental drug in an unsecured environment, but also I was concerned about patient safety. The vaccine protocol called for the drug to be stored at the temperature of liquid nitrogen. I wondered if the vaccine was stable at the higher temperatures? Also, the patients were at risk for drug reactions that might be serious and life threatening, such as anaphylactic reactions. It was obvious that adverse event monitoring was lacking.

In July, after discovering that a monitoring plan had never been developed, I was able to convince Dr. McGee to travel to another clinical site. The site was an oncologist office in Springfield, Missouri. We discovered that the drug was being kept in the refrigerator-freezer, which was located in the staff lounge. Once again, the drug was not being stored at the proper temperatures, and the drug was being subjected to a freeze-thaw cycle. Nor was the drug in a secure location. In fact, there was not any temperature monitoring occurring at all. Institutional review boards—IRBs—are the gatekeepers for the safety and welfare of the human subjects, as mandated by the Federal regulations. However, we found out that the oncologist had never sought local IRB approval, although he himself was an IRB member.

In October, I discovered that the current version of the protocol had never been submitted to the IRB, although it had been in use for 7 months. However, the OU IRB had approved a change in the informed consent, which new title and contact information included St. John's Medical Center. This is significant, because the study was never submitted to the St. John's IRB, even though St. John's IRB chair was also a member of the OU IRB, and he was present when the change was voted on.

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proval was none of the IRB's business, but rather an FDA matter. He instructed us to write protocol amendments that he would get approved to cover us retrospectively.

In November, protocol amendments were submitted to the IRB. They included a change to allow patients to self-inject, increase the size of the trial, change the statistical power, addition of a second drug—GM-CSF—and other modifications to the protocol that were already ongoing. These are but a few examples that patients' safety and welfare were compromised as mandated by the Federal regulations.

I continued to be concerned about the trial. I had already started staying late and reading everything I could find on the FDA website concerning good clinical practices, good manufacturing practices, and good laboratory practices. The more I read, the more alarmed I became. I started asking questions about the manufacturing process and became convinced that the lab was out of compliance as well. Many of the required safety testing for new lots of vaccine had never been completed. Plus, the vaccine was not being manufactured in a sterile environment. Dr. McGee continued to increase enrollment.

Soon thereafter, I started following the chain of command within the medical college and sounding the alarm for what I saw as serious non-compliance with the Federal regulations that were put in place to protect human subjects. Eventually, this led me all the way to the top of the medical college. By the time I blew the whistle in June of 2000, the university had formed a committee that included the dean of the medical college, the director of the office of research, the IRB chair, lab director, Dr. McGee, our department chair and myself. The committee was engaged in acts of cover-up instead of promptly reporting as required by the Federal regulations.

What led me to contact the Office of Human Research Protections? It was the pledge that I took when I became a registered nurse, that I would be a patient advocate. I was haunted by many images, but particularly one image continued to eat at me. It was the informed consent process. By now, I knew that it had been coercive to promise subjects that the melanoma vaccine offered hope of a cure.

Adverse events reporting were practically non-existent. Unfortunately, this sad situation of not reporting adverse events is the same across the Nation as was found by a study conducted by the University of Maryland School of Medicine, Dr. Adil Shamoo.

Today, the university had adopted many positive changes in the way research is conducted. The president of OU is David Boren. I believe in David Boren. In my opinion, he is one of Oklahoma's greatest assets. The university is in the process of implementing a model compliance program and David Boren, the president of OU, is committed to doing so. One of the changes is he has put in place is greater protections for whistle-blowers. I am a graduate of OU and actually, in my own way, I love the university.

Thank you, honorable Senators, for inviting me to speak.

The CHAIRMAN. Thank you very much. We are going to come back with some questions, but we are very grateful for your story, which is an enormously distressing. We will come back for questions.

Dr. Speers.

STATEMENT OF MARJORIE A. SPEERS, EXECUTIVE DIRECTOR, ASSOCIATION FOR THE ACCREDITATION OF HUMAN RESEARCH PROTECTION PROGRAMS; FORMER ACTING EXECUTIVE DIRECTOR, NATIONAL BIOETHICS ADVISORY COMMISSION

Ms. SPEERS. Good morning. I am Marjorie Speers, Executive Director of the Association for the Accreditation of Human Research Protection Programs, AAHRPP, and the former acting executive director of the National Bioethics Advisory Commission, NBAC.

While at NBAC—which had a charter that expired on October 3, 2001—I was the project director for a comprehensive report on human research oversight entitled, "Ethical and Policy Issues in Research Involving Human Participants."

Scientific investigation has enhanced quality of life. In particular, great strides have been made in human research, including the social sciences, the humanities, and the biomedical sciences. As these knowledge areas have developed so rapidly, the research community has been challenged to keep pace with the ethical and moral implications of its work.

NBAC scrutinized the adequacy of the entire system for protecting human research participants. The final report proposed 30 recommendations for changing the oversight system that would ensure all research participants received appropriate protection. Today I will focus on three recommendations that are essential to improving protection.

First, protection should be available to participants in both publicly and privately sponsored research. This recommendation is vitally important, because it responds to concerns about research conducted by Federal agencies that do not follow the Common Rule, or privately-funded research that is not regulated by the Food and Drug Administration. It is ethically indefensible to not protect each and every participant in research.

Implementing such a system, however, is difficult given the current organization of our oversight system. Federal legislation should be enacted to create a single independent Federal office to lead and coordinate the oversight system, and a single set of regulations and guidance should be created that would apply to all types of research involving human participants.

These two recommendations are key pieces to building a comprehensive research oversight system with policies that can be consistently and uniformly applied.

The Common Rule is separately codified in regulation by 15 Federal agencies and followed by two other Federal agencies. However, differences exist among the agencies in how they apply the Common Rule. NBAC stood strongly behind establishing a single independent Federal office with the authority to issue a single set of regulations and guidance. Such an office can be responsive to the changing needs of the research system, revising policy as necessary, and serving as a centralized enforcement authority.

Finally, the NBAC report strongly reinforces creating a culture of concern and respect in the entire research community. An oversight system will succeed to the extent that those involved in human research recognize their ethical obligations to protect participants.

The NBAC report recommends that the Federal Government and professional organizations promote educational training in human research protection, certification for individuals, and accreditation for institutions.

The responsibility for protecting research participants is a shared one. The Government and private sector have important roles to play. I am here today to also testify on behalf of AAHRPP. AAHRPP uses a voluntary, peer-driven, educational model of accreditation. AAHRPP's goals are to recognize institutions that meet high standards and assist the research community in improving its efforts to protect the rights and welfare of research participants. We believe this voluntary self-regulation by the research commu-

nity, along with oversight by an independent accrediting body, is the best strategy for making research as safe as it possibly can be.

AAHRPP's standards meet all regulatory requirements and in some cases exceed them. With these comprehensive standards, we can raise the level of protection beyond the minimal level set by the Government. The standards make clear that protecting research participants is not the sole responsibility of the IRB but a duty shared by everyone who conducts research.

Institutions now have a clear idea of the high expectations that they must meet, and because they know the Government recognizes accreditation as a valuable means for enhancing human research protection, accreditation will be eagerly embraced.

Accreditation has an important place in the overall scheme, improving protection programs, making research safer, and ultimately, preserving and justifying public confidence in research.

Thank you for the opportunity to address the committee.

[The prepared statement of Ms. Speers follows:]

PREPARED STATEMENT OF MARJORIE A. SPEERS

Good morning. I am Marjorie Speers, Executive Director of the Association for the Accreditation of Human Research Protection Programs, known by its acronym, AAHRPP. I am the former acting executive director of the National Bioethics Advisory Commission (NBAC). While at NBAC—which had a charter that expired on October 3, 2001—I was the project director for a comprehensive report on human research oversight entitled “Ethical and Policy Issues in Research Involving Human Participants.” That report was presented to the President on August 20 of last year. In my NBAC capacity, I would like to share several of the major recommendations from that report with you today.

Clearly, scientific investigation has extended and enhanced quality of life, and is one of the foundations of our society's economic, intellectual, educational, and social progress. In particular, great strides have been made in human research, including the social sciences, the humanities, and the biomedical sciences. The American research enterprise is the leader—not to mention, the envy—of the international scientific community.

As these capabilities and knowledge areas have developed so rapidly, the research community has been challenged to keep pace with the ethical and moral implications and operations of its work. NBAC was not alone in its deliberations on this matter; numerous studies addressing participant protection have been conducted by both governmental and private organizations, including the Institute of Medicine, the General Accounting Office, the Office of the Inspector General in the Department of Health and Human Services, the Association of American Medical Colleges, and the Association of American Universities. All of these studies have underscored the need for more careful, thoughtful, systematic human research participant protections.

In preparing its report, NBAC scrutinized the adequacy of the entire system for protecting human research participants, focusing on the current patchwork of regulations described as the “Common Rule” and examining the full range of research with human beings sponsored by both the Federal Government and the private sector. The final report proposed 30 recommendations for changing the oversight system at the national and local levels that would ensure all research participants receive appropriate protections and remove unnecessary burdens. Today, I will focus on three recommendations that are essential to improving protection.

Recommendations 2.1, 2.2, and 2.3 are the crux of NBAC's findings. “Recommendation 2.1: The Federal oversight system should protect the rights and welfare of human research participants by (1) independent review of risks and potential benefits, and (2) voluntary informed consent protection should be available to participants in both publicly- and privately-sponsored research. Federal legislation should be enacted to provide such protection.”

This recommendation is vitally important because it responds to concerns about research conducted by Federal agencies that do not follow the common rule or privately-funded research that is not regulated by the Food and Drug Administration (FDA). In both scenarios, research participants are simply not protected by the cur-

rent oversight system. It is ethically indefensible to not protect each and every participant in research.

Implementing such a recommendation, however, is quite difficult given the current organization of our oversight system, which leads to Recommendations 2.2 and 2.3. “Recommendation 2.2: To ensure the protection of the rights and welfare of all research participants, Federal legislation should be enacted to create a single, independent Federal office, the National Office for Human Research Oversight (NOHRO), to lead and coordinate the oversight system. This office should be responsible for policy development, regulatory reform (see Recommendation 2.3), research review and monitoring, research ethics education, and enforcement.”

“Recommendation 2.3: A unified, comprehensive Federal policy embodied in a single set of regulations and guidance should be created that would apply to all types of research involving human participants (see Recommendation 2.2).”

These two recommendations are key pieces to building a comprehensive research oversight system with policies that can be consistently and uniformly applied. The Common Rule is separately codified in regulation by 15 Federal agencies and followed by two other Federal agencies under an Executive Order and public law, but a number of other Federal agencies that conduct research do not comply with the Common Rule. Even within the 17 agencies that follow the Common Rule, differences exist among the agencies in how they apply the Common Rule. NBAC discovered, for example, that regulatory coverage for vulnerable populations in research, such as children, is inconsistent across the Federal Government, which is particularly worrisome given that most Federal departments conduct research involving individuals who are in some way vulnerable.

NBAC stood strongly behind the need to establish a single, independent Federal office with the authority to issue a single set of regulations and guidance. This recommendation is not meant as a criticism of the Office of Human Research Protection within the Department of Health and Human Services; rather, NBAC recognizes the need for a Federal office to exist independently and outside of a Federal department or agency that sponsors research and be responsive to the ethical issues of all fields of research, not just those of primary concern to the Department of Health and Human Services. Such an office can be responsive to the changing needs of the research system, revising policy as necessary, and serving as a centralized enforcement authority. Currently there is no effective means to do so; the agencies who are signatories to the Common Rule have not been able to make changes to it in the last 11 years, even though the need for changes has existed.

Regulations should address basic ethical standards that are common across all research types, such as informed consent, vulnerability, and privacy and confidentiality. In addition, guidance should be offered that assists in interpreting basic regulations in different areas of research. A wide variety of research, from clinical trials to social science methods, is currently regulated under the same set of Federal rules. However, these rules were originally written at the National Institutes of Health and do not always appropriately address the ethical issues in research outside of the biomedical context. With fewer and flexible regulations and more appropriate guidance on how to apply the regulations to different types of research, the oversight system recommended by NBAC would be more responsive to investigators’ and participants’ concerns.

While NBAC’s primary goal was to make recommendations that would improve protections for research participants, it was also interested in identifying ways to reduce the unnecessary burdens within the current oversight system. Federal regulation and guidance should require ethics review and oversight that is commensurate with the nature and level of risk in the research. For example, NBAC recommended that the regulations should permit institutions to use approval procedures other than full IRB review when research involves no greater than minimal risk.

Adopting NBAC recommendations would go far in ensuring the protection of research participants in a manner that encourages and facilitates research that is consistent with accepted ethical principles.

Finally, the NBAC report strongly reinforces the need for a culture of concern and respect in the entire research community. An oversight system will succeed to the extent that those involved in human research recognize their ethical obligations to protect participants. The NBAC report recommends that the Federal Government and professional organizations promote educational training in human research protection, certification for individuals, and accreditation for institutions. If this cultural shift can occur, we will arrive at a comprehensive, flexible system based on ethical principles and focused on ethically substantive requirements that should maximize protections for research participants.

The responsibility for protecting research participants is a shared one. The Government and the private sector, universities in particular, have important roles to play. I'm here today to also testify on behalf of a new, private sector organization, AAHRPP.

From my years of overseeing research, to my role at NBAC, to my current position at AAHRPP, it has become clear to me that there is no single problem with the current oversight system for protecting research participants crying out for urgent repair, but there are several problems that need to be corrected in a comprehensive manner. This is a time for a fresh start, and for us to examine all aspects of the oversight system.

In addition to the three major recommendations that I outlined from the NBAC report, the commission took a stand in favor of accreditation: "Recommendation 3.4: Sponsors, institutions, and independent institutional review boards should be accredited in order to conduct or review research involving human participants. Accreditation should be premised upon demonstrated competency in core areas through accreditation programs that are approved by the Federal Government."

AAHRPP uses a voluntary, peer-driven, educational model of accreditation. By requiring institutions to meet an explicit set of standards for protection, AAHRPP's goals are to recognize institutions that meet these high standards and assist the research community in continuously improving its efforts to protect the rights and welfare of research participants. We believe that voluntary self-regulation by the research community, along with oversight by an independent accrediting body, is the best strategy for making research as safe as it possibly can be.

The history of accreditation shows that it is successful when it arises from the concerns of professionals engaged in the field, such as in higher education. AAHRPP was founded by seven organizations that bring diverse perspectives to this new enterprise: the Association of American Medical Colleges, representing medical schools, teaching hospitals, and academic societies; Association of American Universities, representing major research-intensive universities; Consortium of Social Science Associations, advocating on behalf of social and behavioral science organizations; Federation of American Societies of Experimental Biology, the Nation's largest coalition of biomedical research organizations; National Association of State Universities and Land Grant Colleges, representing public universities and land-grant institutions; National Health Council, representing patient and health-related groups; and Public Responsibility in Medicine and Research, respected for its more than 3 decades of improving ethics in both medicine and research through education. The views of research participants, the public, investigators, and sponsors of research have been represented since AAHRPP's inception, and that diverse representation continues on our 21-person board of directors, our council on accreditation, and among our site visitors.

Now is the time for accreditation to take hold. The time is right for several reasons: first, the Government has provided leadership and clear guidance that accreditation has real potential for improving performance and quality, and that it should be undertaken. Second, the Government has exercised its enforcement options. Highly publicized shutdowns of large research programs at academic institutions in the past several years captured the attention of the research community—and the Nation, and made it clear that Federal regulations for protecting research participants were to be taken seriously.

Over the last year, with recognition by the research community of the need to improve human research protections and the desire to move deliberately and swiftly, AAHRPP has taken governmental policy and developed it, with the input from a diverse range of professionals and the public, into a clear set of accreditation standards. As the NBAC report states: "The choice of standards for these [accreditation and certification] programs and the criteria for evaluating whether an institution has met them are critically important."

AAHRPP's standards meet all regulatory requirements and, in some cases, exceed them. With these comprehensive standards, we can raise the level of protection beyond the minimal level set by the Government. AAHRPP's standards are significant in several other respects: they are broad and flexible so that they will be meaningful to a full range of research types; certainly in clinical research, but also in social science, historical, and business research. The standards can be applied in a variety of research settings, including universities, hospitals, Government agencies, and independent institutional review boards. Finally, the standards make clear that protecting research participants is not the sole responsibility of the IRB, but a duty shared by everyone who conducts research. Entities seeking accreditation must meet standards that address the obligations relating to the organization, IRB, investigator, sponsor, and participant. This is an important point, as much of the dialogue and debate on human research protections has focused on the role and function of

the IRB. While there is no doubt of the key role played by IRBs, AAHRPP believes strongly that the protection of human research participants is a collective responsibility of the entire research community, beginning with institutional leadership and extending to the most junior staff.

With the introduction of these standards, institutions now have a clear idea of the high expectations they must meet. And because they know the Government recognizes accreditation as a valuable means for enhancing human research protections, accreditation will be eagerly embraced.

In closing, I'd like to say that the accreditation of human research protection programs is not a panacea. But in conjunction with other efforts underway and other recommendations yet to be implemented, accreditation has an important place in the overall scheme. The benefits of accreditation seem clear: improving protection programs across the entire research community, making research safer and reducing unnecessary harm, and ultimately, preserving and justifying public confidence in research.

Thank you for the opportunity to address the committee.

The CHAIRMAN. Thank you very much.

Dr. Johnson.

STATEMENT OF DR. CHARLES A. JOHNSON, ASSOCIATE DIRECTOR OF SPECIALTY BIOTHERAPEUTICS, GENENTECH, INC., ON BEHALF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION

Mr. JOHNSON. Good morning, Mr. Chairman, members of the committee.

My name is Dr. Charles Johnson. I am Associate Director of Specialty Biotherapeutics at Genentech, which is a leading biotechnology company headquartered in South San Francisco, California.

I am here today representing the Biotechnology Industry Organization. BIO represents more than 1,000 biotechnology companies, academic institutions, and State biotechnology organizations.

Thank you, Mr. Chairman, for holding this hearing on such an important issue, which is how to facilitate critical medical research while effectively protecting those who voluntarily participate.

As you and your colleagues examine this issue, I urge you to remember two critical facts. First, participants in research are volunteers, meaning that we must do all we can to ensure that they have the utmost confidence that they will be protected. Second, medical research has and will continue to lead to cures and treatments for millions of Americans suffering from disease.

Mr. Chairman, medical research is a heavily regulated activity. Our products and manufacturing processes are regulated by the Food and Drug Administration. Our research protocols are reviewed and scrutinized by institutional review boards. Moreover, virtually all States have developed regulations that affect research. In addition, the HIPAA privacy rule imposes a new layer of review and oversight over our research.

Despite this extensive regulation, some have called for additional restrictions to be instituted relating to consent, IRB accreditation and review, and conflicts of interest. From many different perspectives, reform of the existing system is not only necessary and desirable, but it appears inevitable.

Based on BIO's analyses, we have identified the following issues. There are multiple and overlapping layers of review. There is an already overwhelmed IRB system. There are rules regarding review of research involving human participants that are inappropriate for

research involving medical archives and data. There are differing State laws. And finally, there are perceived conflicts of interest.

The current regulatory system applies multiple overlapping layers of review for sponsors of every clinical protocol. Trials that take place in several locations must be reviewed by several different bodies. Each can require changes in trial design, the informed consent form, or any other protocol component.

An additional complication is the HIPAA privacy regulation which governs the use and disclosure of medical information. BIO believes that Congress should eliminate these multiple separate legal reviews. Researchers should be allowed to use patient information without authorization where those researchers either secure informed consent or obtain a waiver of authorization by an IRB or privacy board.

We note that the HHS recently proposed modifications to the HIPAA privacy rule that would streamline the requirements for waiver of authorization. BIO supports these proposed changes, and we urge the HHS to adopt these modifications in its revised final rule.

In addition, BIO believes that IRBs should be held accountable, and therefore supports the development of a system of accreditation. Currently, research studies are reviewed using the same criteria regardless of the type of risk faced by the research participant. BIO supports an alternative approach that makes regulatory oversight commensurate with the risk. Such a system would establish one set of requirements for research that involves intervention and a separate set of requirements tailored to the unique issues raised by research using medical records and tissue archives.

This new framework would be applicable to all research regardless of its funding resource. Last year, the National Bioethics Advisory Commission also endorsed this notion.

A related problem is that researchers are subject to a patchwork of different and often inconsistent State laws. This confusing regulatory environment will slow important research efforts. BIO believes that Congress should create one national, uniform set of rules governing research. These national standards would allow researchers to apply strong informed consent, privacy, and other research protection rules that are consistent across all States.

Finally, there is a persistent perception that the presence of private money in the health care setting creates conflicts of interest. BIO strongly believes that the best way to both protect patients and the integrity of research is to assure that research protocols are independently reviewed and that all financial interests are disclosed. In this regard, BIO and the National Bioethics Advisory Commission are in agreement.

Mr. Chairman, thank you for this opportunity to testify. BIO companies believe that it is critical to make sure that research participants are protected; yet we must also ensure the continuation of valuable, potentially life-saving research. Decades of responsible science have shown that protecting research participants and promoting research are mutually attainable. BIO looks forward to working with the committee as it pursues both of these goals.

Thank you.

[The prepared statement of Charles A. Johnson, M.D. follows:]

PREPARED STATEMENT OF CHARLES A. JOHNSON, M.D.

Good morning, Mr. Chairman and members of the committee. My name is Dr. Charles Johnson. I am associate director of specialty biotherapeutics at Genentech, Inc., a leading biotechnology company headquartered in South San Francisco, California. I am here today representing the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions and State biotechnology centers in all 50 States and 33 other nations. BIO's members are involved in the research and development of medical, agricultural, industrial and environmental biotechnology products.

Most of the hard work in our industry is directed toward research on currently unmet medical needs: new therapies and cures for various cancers, Alzheimer's and Parkinson's diseases, diabetes, heart disease and hundreds of other debilitating and life-threatening illnesses.

Thank you, Mr. Chairman, for holding this hearing on such an important issue: how to effectively protect those who voluntarily participate in our research while, at the same time, facilitating critical medical research. As you and your colleagues examine this issue, I urge you to remember two critical facts:

First, participants in research are volunteers, meaning that we must do all we can to ensure that they have the utmost confidence that they will be protected.

Second, medical research has and will continue to lead to cures and treatments for millions of Americans suffering from diseases. One-hundred-seventeen biotechnology products have helped a quarter-billion people worldwide thus far, and another 350 biotech medicines targeting more than 250 diseases are in late stage development. Many of these are diseases that are currently incurable.

Much attention has been given lately to issues surrounding the protection of the volunteers who participate in our research. As you are already aware, Mr. Chairman, medical research is a heavily regulated activity—our products and manufacturing processes are regulated by the Food and Drug Administration (FDA), and our research protocols are reviewed and scrutinized by institutional review boards (IRBs) under an extensive set of Federal regulations governing research (the Federal Common Rule). Moreover, virtually all States have developed regulations that affect research. In addition, the HIPAA privacy rule imposes a new layer of review and oversight over our research.

Despite this extensive regulation, some have called for additional restrictions to be instituted relating to consent, IRB accreditation and review, and conflicts of interest.

From many different perspectives, reform of the existing system is not only necessary and desirable, but appears inevitable. In light of this, BIO companies have spent considerable time evaluating the existing system of research oversight. Based on this analysis, we have identified several key concerns and areas for improvement. They are:

Multiple and overlapping layers of review, leading to confusion and inefficiency for participants as well as research sponsors;

New regulations that will increase the burden on an already overwhelmed IRB system;

An existing framework for review of research involving human participants that is inappropriate for research involving medical archives or data;

Differing State laws govern and complicate the form of research review and format of consent required in each State; and

A strong and persistent perception that the presence of private money in the health care setting creates conflicts of interest in researchers that may affect results and the quality of care provided to research participants.

Multiple Layers of Review

The current system of research review relies heavily on IRBs. Historically, they have filled the important role of providing independent review of research projects. However, the current regulatory system applies multiple overlapping layers of review for sponsors of every clinical protocol. Specifically, FDA regulations require the sponsor to obtain review by an IRB, and each investigator affiliated with an academic institution must have its IRB separately review and approve every aspect of the research protocol under Federal regulations that apply to institutions that receive Federal grant money. Consequently, trials that take place in several locations must be reviewed by several different review bodies. Each can require changes to trial design, the informed consent form, or any other protocol component. This adds enormous complexity and expense to a research project.

An additional complication is the HIPAA privacy regulation governing the use and disclosure of medical information. That regulation adds an entirely new authoriza-

tion process to the informed consent already required from every research participant and/or data subject. It requires that researchers get an individual's authorization—or a waiver of authorization from an IRB or privacy board—to access and use protected health information for research purposes. The IRB's review of this issue is in addition to its consideration of the other risks present to research participants.

Thus, two distinct assents are now required of each research subject: informed consent to participate in research and “authorization” to disclose and use an individual's protected health information in research under the HIPAA privacy regulation.

As to the overall issue of the growing multiple layers of review, BIO believes Congress should eliminate the multiple separate legal reviews currently required for clearance of a sponsored clinical research protocol. Mechanisms should be developed to centralize and streamline review of research projects. In addition, researchers should be allowed to use patient information without authorization where researchers (1) secure individuals' informed consent or (2) obtain a waiver of consent by an IRB or privacy board, in whole or in part, where waiver is warranted under existing law. In addition, we support modifying the criteria for waiver of consent/authorization for use of patient data and archival information both in the privacy rule and under the current Common Rule to enhance access to much-needed data where the confidentiality risks present to the individual are minimal.

In this regard, we note that HHS recently proposed modifications to the HIPAA privacy rule that would simplify and streamline the requirements for authorization by IRBs and privacy boards. BIO supports these proposed changes as an important first step in eliminating unnecessary and inappropriate regulatory hurdles for the conduct of research, and we urge HHS to adopt these modifications in its revised final rule. Without these changes, the existing waiver of authorization standard, in particular, is unworkable and will have a significant adverse impact on research activities.

In addition, since IRBs play such an important role in the research oversight system, BIO believes they should be held accountable for meeting their responsibilities. Some have recommended that a system of accreditation for IRBs be developed. BIO is intrigued by the concept of IRB accreditation and would be supportive of exploring the issues involved.

Review Commensurate with Risk

Currently, research studies are reviewed using the same criteria regardless of the type of risk faced by the research participant. For example, a research study that entailed testing a drug on individuals will be regulated the same way as a study that relied only on a review of medical records. This process does not acknowledge the different types of risk faced by the research subjects in each study. Participants in the first study will confront safety risks, while subjects in the second study face risks related almost entirely to confidentiality.

The regulatory structure stems from the history of our oversight system that based Federal review on factors other than the risk to the research participant, such as presence of Federal funding or regulation. BIO believes that this paradigm is no longer appropriate—for researchers or research participants. As we learn more about how genomic information can be used to cure disease, medical records review and archival research will grow in importance.

Thus, BIO supports an alternative approach that makes regulatory oversight commensurate with the risk to the research participant. That type of system would establish one set of requirements for research that involves intervention or interaction with individual research participants and a separate set of requirements tailored to the unique issues raised by research using medical records and tissue archives. This new framework would be applicable to all research, regardless of its funding source. It is important to note that in a report issued last year, the National Bioethics Advisory Commission (NBAC) made a similar observation, and endorsed the notion that review should be commensurate with the types of risk presented by the research.

Differing State Laws

A related problem is that researchers are subject to a patchwork of different, and sometimes inconsistent, State laws. Although there are extensive Federal rules regarding research, State laws govern issues such as the form of review and format of additional documentation of consent.

This is often problematic for researchers. For example, new State laws pertaining to genetic analysis are quite restrictive, requiring additional separate consents and imposing onerous requirements regarding the use and retention of tissue and blood samples that sometimes are inconsistent with FDA requirements.

A 1999 study of State health privacy laws showed the vast differences among the States. In addition to existing differences, State laws in this area are in flux. During

the 2000 State legislative session, 26 States debated laws concerning privacy. This turbulent environment will slow important research efforts.

It is important to note that the differences among States do not seem to start from differences in the level or degree of protection, but reflect different State legislatures' views of the specific procedures or requirements for accomplishing the same objective. Nonetheless, the requirements and penalties are different enough to require every researcher to hire lawyers to assure compliance with the laws of more than 50 States and local jurisdictions in designing informed consent documents for a multi-state trial.

To remedy this problem, BIO believes that consideration should be given to creating one national, uniform set of rules governing research. National standards would allow researchers to create informed consent and other procedures that will be legal in all States. These Federal research standards should pre-empt State laws that create conflicting obligations regarding research participants from different States.

Conflicts of Interest

There is a strong and persistent perception that the presence of private money in the health care setting creates conflicts of interest in researchers that may affect results and/or the quality of care provided to research participants. This perception has the potential to damage the public's trust in biomedical research.

We must take steps to maintain public confidence. However, it is important to remember that the tremendous investment by the private sector over the past 2 decades has led to remarkable medical breakthroughs. Government policy to encourage private investment has been a major factor in the development of a biotechnology industry in the United States that is the envy of the world.

The best ways to both protect patients and the integrity of research is to ensure that research protocols are independently reviewed and that all financial interests are disclosed. We understand that the academic institutions are in the process of carefully reviewing conflict of interest issues and are attempting to generate a unified position and set of policies regarding financial interests. In the meantime, BIO agrees with the direction of the NBAC recommendations, which is to focus the discussion in a way that encourages disclosure of financial relationships between and among researchers, investigators and IRBs, but does not prohibit, nor otherwise impose, rigid restrictions on the existence of such relationships.

Conclusion

Mr. Chairman, we believe that it is appropriate to review the existing regulatory structure for research and urge that consideration be given to BIO's four key principles: (1) eliminate multiple separate levels of review; (2) modify the regulatory framework so that review is commensurate with the type of risk involved for the research participants; (3) preempt State laws that create conflicting obligations; and (4) work with academic medical centers and other affected entities and individuals to develop an approach for addressing real and perceived conflicts of interest.

BIO companies believe that it is critical to make sure that, despite the changes in our research infrastructure over the years, participants continue to be protected. We firmly believe that addressing these key issues described above will enhance the level of protections we can guarantee participants in our research projects.

In protecting our research participants, we must also ensure the continuation of valuable—potentially life-saving—research. We are fortunate to live in an era of enormous promise as scientists begin to access a vast library of genetic information with the goal of improving our medical interventions. Decades of responsible science have shown that protecting research participants and promoting medical research are mutually attainable.

BIO looks forward to working with the committee as it pursues both goals.

Thank you.

The CHAIRMAN. Thank you very much.

Dr. Charles.

STATEMENT OF DR. P. DAVID CHARLES, ASSISTANT PROFESSOR OF NEUROLOGY, VANDERBILT UNIVERSITY MEDICAL CENTER, ON BEHALF OF THE NATIONAL ALLIANCE OF MEDICAL RESEARCHERS AND TEACHING PHYSICIANS

Dr. CHARLES. Thank you, Mr. Chairman and members of the committee.

I appreciate the opportunity to briefly tell you of my experiences as a clinical investigator and my views on patient protection. In my role as director of the Movement Disorders Clinic at Vanderbilt University, I work as a physician treating patients with Parkinson's disease and related disorders, and spasticity, which affects children and adults who have suffered injury to the brain or spinal cord. In my role as neurology residency program director, I teach young physicians who are training to become neurologists, and I am responsible for their educational program.

The work that I do day-to-day, however, is clinical trials to develop new drugs, new biologics, and new medical devices for the treatment of Parkinson's disease and related disorders in spasticity.

In the past, I took leave from my health practice to serve as a health policy fellow on the staff of this committee, under the direction of Senator Frist, and while here, I would often meet people with our Government who felt that technology in health care was a bad thing, because technology in health care would increase the cost of health care.

This was surprising to me as a physician, because I knew that new technologies in health care were responsible for so many great advances in health care—speeding diagnosis, less invasive treatments, and improved productivity and quality of life.

Following my experience here in the U.S. Senate, my family and I traveled to France, where I served as a Fulbright Scholar, conducting research on Parkinson's disease to bring a new line of treatment and investigation back to Vanderbilt.

Upon my return to the United States, my colleagues and I formed the National Alliance of Medical Researchers and Teaching Physicians. This is a group of physicians and researchers who advocate for the benefits of technology in health care—the electronic medical record, technologies that speed basic science research, improve diagnostic procedures and equipment, implanted medical devices, and telemedicine. I felt this group was needed because I learned that many people inside our Government do not understand that new technologies improve our Nation's health care and the health of our Nation and that clinical research that involves human subjects as how those new drugs, new biologics, and new medical devices are brought to everyday use.

At Vanderbilt, I have had the opportunity to serve as principal or co-investigator in over a dozen clinical trials, so I present to you the views of a rank-and-file clinical investigator actively conducting clinical trials. To answer the question of this hearing, in short: are the current protections adequate? Yes. Are they disorganized, poorly coordinated, and in need of improvement? Yes.

The National Alliance of Medical Researchers and Teaching Physicians supports a single, uniform system for federally-funded and regulated research that involves human subjects that follows these basic principles: A comprehensive and uniform set of Federal protections; strong, informed and independent oversight by institutional review boards; effective privacy protections that do not prevent important archival research and quality improvement; and strong guidelines governing conflicts of interest that require full disclosure of such arrangements.

Embracing technology in health care will allow terrific improvements in the quality of care and dramatic cost savings and improve patient quality of life through the following: Improving the ability to coordinate care across specialty fields from both physical and mental health perspectives; ensuring the use of evidence-based practice of medicine; and dramatically reducing medical errors.

We all recognize that safeguarding the health of those who serve as participants in clinical trials and preserving the integrity of research is essential. These are common goals supported by the clinical research community, the general public, and by members of this committee, I am sure.

The joint challenge of the medical profession and the public policymakers is to strengthen safeguards without creating new regulations so burdensome that they make it impossible to complete vital research.

Society loses if regulations to protect the public become obstacles to serving the public. That principle applies to the issue of protecting the health of human participants in clinical trials and to the issue of preventing conflicts of interest in the research community.

I would just add that clinical researchers share this committee's urgency to reinforce the safety and integrity of clinical research practices. Clinical research was essential to the medical breakthroughs that made the last century the pivotal century in health care and made America's health care the best in the world. To build on that record in the 21st century, we need the full confidence of the American people.

Mr. Chairman, that concludes my remarks. I look forward to questions.

[The prepared statement of P. David Charles, M.D. follows:]

PREPARED STATEMENT OF P. DAVID CHARLES, M.D.

Mr. Chairman and members of the committee, my name is David Charles. I am a physician and Director of the Movement Disorders Clinic and Neurology Residency Training Program at Vanderbilt University Medical Center. I also serve as chairman of the National Alliance of Medical Researchers and Teaching Physicians, a coalition of doctors, scientists and health care providers dedicated to the advancement of medicine through technology. I am testifying today in my role as chairman of the National Alliance of Medical Researchers and Teaching Physicians.

It is a special privilege for me to comment on the important issue before this committee and I greatly appreciate the opportunity.

As a doctor and an American, I am gratified that the Public Health subcommittee includes some of the most distinguished names in the U.S. Senate. I am delighted that this committee includes my fellow Tennessean and clinical researcher, Senator Frist.

My comments represent the perspective of someone who works full-time in clinical research and teaching. And I might start by asking the semi-rhetorical question: "What is clinical research?" For our purposes here, let's think of clinical research as the phase of medical science where the discoveries of the laboratory meet the realities of the human body.

No drug, no medical device, no surgical procedure will ever prove its value to cure disease or ease suffering until it has been tested on people. Yet the investigation of new treatments on humans, even if the testing may lead to a cure of a devastating disease, arouses our sensitivities and concerns, as well it should.

We all recognize that safeguarding the health of those who serve as subjects in clinical trials and preserving the integrity of the research process is essential. These are common goals supported by the clinical research community, the general public, and, I am sure, by the members of this committee.

In terms of the issues under consideration by the committee, I might paraphrase the oft-quoted Mr. Churchill and say: “Never have so many disagreed so little about so much.”

But, I am also reminded of the cynical summary Calvin Coolidge gave one Sunday afternoon of a sermon he had heard that morning.

“The preacher talked about sin,” said Coolidge. “He was against it.”

Today, we are all against exposing people involved in clinical trials to excessive risk. We are all opposed to violating the privacy of medical data during the research process. And certainly, we are all concerned about potential conflicts of interest among those who conduct clinical research and the health care companies that sometimes fund such research.

But, being opposed to those things is the easy part. Improving the safeguards already in place is much more complicated and difficult.

We have to recognize, for instance, that clinical researchers testing and refining new drugs or medical devices have to work closely with the companies that created those products. Vital medical research couldn’t take place without that kind of co-operation.

Can we still conduct clinical research that might involve potential conflicts of interest? We can so long as there are strong safeguards in place that protect the outcome of the research and the well-being of the human subjects.

The joint challenge of the medical profession and public policymakers is to strengthen safeguards without creating new regulations so burdensome that they make it impossible to complete vital research. Let’s not throw the baby out with the bath water.

And let me emphasize—my concern about burdensome regulations is not code for eliminating vigorous oversight, by Government and by our own profession. Like most doctors, I recognize the need to have others looking over every step of my work during a clinical trial to safeguard against potential conflicts of interest and to protect the health, well-being, and privacy of the people participating. That kind of scrutiny comes with the territory in our profession.

But, society loses if regulations to protect the public become obstacles to serving the public. That principle applies to the issue of protecting the health of human subjects in clinical trials and to the issue of preventing conflicts of interest in the research community.

When something goes dangerously wrong in a clinical research effort, it gets public attention and feeds the appetite for more regulations. That is understandable. For the sake of perspective, though, let’s remember that we are talking about a relative handful of failures against a century’s worth of successes.

The abomination of the Tuskegee Syphilis Study still taints public attitudes toward human testing, 30 years after the study was ended. The tragic death of 18-year-old Jesse Gelsinger during a gene transplant study in 1999 left us asking once again, how can we make the process even safer?

Much of the regulations and governing philosophy already in place is effective. All of it is well-intentioned. But the system still gives conflicting signals to researchers and the hybrid mix of agencies involved makes it difficult to rationalize those signals. The result can sometimes be research paralysis.

The practical reality is that it can be very, very difficult to navigate the extreme caution and regulatory burden necessary to gain approval to launch a clinical trial. Once the clinical trial is approved, however, it can be even more difficult to actually identify people willing to participate in an investigation and to find the necessary number of people with a particular disease that meet the requirements of the clinical trial. The thicket of reviews required for a clinical trial can be dense to the point of being impenetrable. At times, I feel that I need a second career just to handle the paperwork.

As a result, clinical trials simply aren’t being done at the rate we all recognize that they should. This is an example of regulations having the right intent, but the wrong results. And it’s just one example.

I think this committee could do this Nation a great service by simplifying the clinical research regulations and clarify who has responsibility for enforcing them. I believe this can be done at the same time you tighten those regulations and promote even more safety and integrity in the research process.

The National Alliance of Medical Researchers and Teaching Physicians would like to commend the Federal Department of Health and Human Services and the General Accounting Office for the study they have already made of this issue. The Alliance has also given this our serious attention. As a result, we support the following principles for any new Federal legislation:

- A comprehensive and uniform set of Federal protections.

- Strong, informed, and independent oversight by Institutional Review Boards (IRBs).
- Effective privacy protections that do not prevent important archival research.
- Strong guidelines governing conflicts of interest that require full disclosure of such arrangements.

As a first principle, we strongly recommend a comprehensive and uniform set of Federal laws assuring that all research is designed and carried out in accord with high ethical standards for protecting human subjects from research risks. As you know, the Federal Government now relies on what's known as the "Common Rule."

This is a set of requirements endorsed by 17 Federal departments and agencies. The Common Rule is the closest thing the Federal Government has to a comprehensive, uniform set of regulations covering human testing. In practice, however, individual agencies routinely depart from the Common Rule and make policy on their own, to meet what they see as special circumstances. Today, investigators often face overlapping, confusing, and sometimes contradictory regulatory systems.

The Common Rule's provisions for protecting human subjects from the risks of interventional research should be clarified. Equally important, any proposed legislation should apply to all federally-sponsored or regulated research with humans.

The Common Rule badly needs the momentum it would get from being codified into Federal law. These statutes should include specific rules for gaining the informed consent of research subjects, and define the circumstances under which waiver of informed consent is justified. However, there are legitimate concerns with codifying the Common Rule, and we should be careful to ensure that the standards under any legislation be flexible and able to adapt as science continues to evolve.

Any set of rules is only as good as their enforcement. We recommend that the enforcement and interpretation of new codified Federal standards for interventional research be handled primarily by strengthened institutional review boards (IRBs).

The new institutional review boards would have clearer authority and more demanding standards for board membership. We recommend that these new boards be overseen by the existing Office of Human Research Protection.

These IRBs would be responsible for reviewing and approving or rejecting all proposed protocols for interventional research.

To protect the independent judgment of these boards, the review fees of the boards could not be paid with equity interest in the company sponsoring the proposed research, or as a share of any royalties arising from the research.

In the important area of protecting the privacy of the medical data of individuals, we support the Secretary of Health and Human Services' March 27, 2002, proposal to modify the Federal medical privacy rule. We support a continued effort to improve guidelines for research that analyze databanks of medical records, health benefit claims and archives of biological materials and genetic information. The goal should be to establish mechanisms that minimize the risk to individuals' privacy while protecting the ability to conduct much needed research.

Consumers are already painfully aware of the vulnerability of their personal data. The perceived lack of data security is the biggest drawback to doing transactions on the internet. This only reinforces the need to take the initiative in guaranteeing privacy protection for medical data used in research.

One final, but major point, addresses the sensitive issue of conflict-of-interest in the conduct of research.

In the belief that full disclosure is the best form of protection for all concerned, we recommend that prior to evaluation of a research protocol, Federal law should require:

- That the research investigators disclose to the appropriate institutional review board what arrangements have been made for compensation.
- That researchers must disclose up-front whether or not they or their immediate families have a proprietary interest in the outcome of the proposed research.

In this area of avoiding conflicts-of-interest involving compensation, we also believe it would be beneficial for the IRB to be authorized to consider whether:

A.—The arrangements for compensating researchers or their proprietary interests in the research might influence their judgment as to the risk faced by a human subject participating in the research.

B.—Whether the arrangements for compensating human test subjects might unfairly induce some prospective subjects to accept unreasonable risks.

I would just add that clinical researchers share the committee's urgency to reinforce the safety and integrity of clinical research practices. Clinical research was essential to the medical breakthroughs that made the last century the pivotal century in health care and made America's health care the best in the world.

To build on that record in the 21st century, we need the full confidence of the American public.

Thank you.

The CHAIRMAN. I want to thank all of you. It will be wonderful if we can take all the different points of view that have been expressed here and come out with a recommendation that incorporates your comments. But we want to let this panel know, and others, that we are enormously interested in trying to work through this process to avoid the kinds of egregious situations that we have seen, and also with the understanding that, I think, we have on this committee—that this is the century of the life sciences. Whatever progress we saw made in physics and math in the last century, it is here and now with the life sciences, and this is going to be the cutting edge in terms of health and I think, a wide variety of other areas, not just the health of our fellow citizens, but many different aspects of our society.

So we have an important responsibility to try to get this right, and we need help and assistance, and all of you have given this a good deal of thought, so we are going to be drawing on you for your experience.

We will have 8-minute rounds, and I will ask staff to keep track of the time.

Cherlynn, some people want to rely solely on voluntary standards to protect subjects. Do you feel that voluntary standards would prevent the kinds of abuses that you have described?

Ms. MATHIAS. No, I do not. I believe that it must be mandatory. For one thing, I do not think that people will do voluntary standards. For example, when we think back to JAHCO, the joint commission, it was not until the joint commission was tied to Medicare that people really got on board with joint commission wholeheartedly. I think the standards must be mandatory, and that also, if it were voluntary, it would take way too long to implement, and most places simply will not do them.

The CHAIRMAN. Is it your sense that the good research areas would comply, and you are concerned that some of the others might not, and they are the ones that you would be the most concerned about?

Ms. MATHIAS. Yes. I think the largest institutions and the ones who have already faced regulatory problems, such as Oklahoma University, Duke, and a variety of other places, would be the first to sign up for voluntary compliance and accreditation. But I think that most community facilities would bow out of those.

The CHAIRMAN. Your story is amazing for so many different reasons, but the fact is you notified so many different individuals all the way up the process and the system—I count at least four different levels—and still, you were shunted aside and not taken seriously, which is obviously a matter of enormous concern.

Do you think the violations of the human subject protection that you described are unique at the University of Oklahoma, or do you think there are similar problems at other universities?

Ms. MATHIAS. I think they are very widespread, and I think it is not just at universities, but in community settings as well. For example, just in the last several months, I have become aware of doctors who purposely put people in trials who were ineligible and gave them wrong doses of drugs on purpose because they were planning to just treat the patient.

Physicians have a very difficult time distinguishing between patients and medical practice and research and study subjects. That ground becomes very hazy to them.

I am also aware of instances that have occurred in the last 6 months in devices where experimental devices were implanted in people's hearts, and they were never told that they had had experimental devices placed in their bodies until after the fact; so they were never given informed consent properly to have those experimental devices implanted.

I think the problems are widespread, and I see them on a day-to-day basis, a lot of these problems, repeated over and over again.

The CHAIRMAN. What is your sense about how the financial conflicts of interest, either for the doctors conducting the trial or for the university, contribute to the problems you have described? In many instances, the doctors can receive a benefit and the university as well.

Ms. MATHIAS. The conflicts of interest in the university setting—more and more of the universities are relying upon moneys generated for research and development. Even at the University of Oklahoma, Dr. McGee was planning to make quite a bit of money from patenting his vaccine, and I think that played a part.

But conflicts of interest are even deeper than that.

The CHAIRMAN. Played a part in what? In keeping the irregularities—

Ms. MATHIAS. Right, in keeping the irregularities. But even in my own instance, I face conflicts of interest every day. My performance is evaluated on how many people I enroll for clinical trials—not by the quality of the data that I collect. Rather, every month, I have to prove that I have enrolled so many people in clinical trials, and that puts me in a very conflicted situation when I do informed consent, because that is what I am being judged on—by how many people I get on trial. Sometimes, that puts you in a situation where you are trying to talk people into going on clinical trials, and you should not be talking them into anything.

The CHAIRMAN. The whole purpose of informed consent is to give knowledge to the individuals and make them completely aware of both the potential advantages and the potential side effects of this. And you are saying that your evaluation is of a number of people who are involved, and where you might give balanced information, there is a financial or job performance incentive to enroll more people.

Ms. MATHIAS. It is something that I even struggle with myself, and I really try to be ethical, but there are times when I am at the end of the month, and I have not met my quota, and I think, "Oh, my God, I have not met my quota of patients that I am supposed to enroll this month." It puts us in a very conflicted situation.

The CHAIRMAN. We did not get into the kind of harassment that you faced, which was significant, and I did not get into the work that David Boren, our former colleague, now president of Oklahoma University, did when he learned about the ethical abuses committed and instituted a number of measures to try to deal with those. You have referenced that in a very positive way, and I want

the record to show both points, but I want to move on if I can to Dr. Speers.

The commission reported that the current overlap of Federal requirements for research subject protections can be confusing to researchers and patients. How do you propose to minimize the overlap without compromising patient safety? As you remember, the initial panel that we had supported going back a long time ago, we had a commission made up of ethicists. Their power was just to propound ethical recommendations in the Federal Register, and all the various agencies accepted those. Then, Secretary Califano felt that each of the various Government agencies and institutions should have their own panel, and we have seen a lot of these emerge with the kind of challenge that Dr. Johnson has pointed out, with overlap, duplication, confusion.

But this is what I want to get to. What did the commission report concerning the overlap of the requirements which can be confusing? How do you propose to minimize that confusion?

Ms. SPEERS. The commission was concerned because it heard from various groups—from institutions, IRBs, and investigators—that the current set of regulations was confusing. The commission recommended that there be a single set of regulations and guidance and that the ethical principles and standards that are common to all research should be codified in regulation, and then, regulations should be supplemented with guidance that would help investigators and IRBs interpret how the regulations would be applied to different types of research.

The CHAIRMAN. So effectively, you have an overarching responsibility, and particular implementations for different types would be carried out by the various agencies that have responsibility for different types of research; is that it?

Ms. SPEERS. Yes, that is correct. The commission was concerned about two things. One was that the regulations and guidance would be pertinent to the types of research that were being conducted, and they wanted to focus attention on the research that had the greatest risk associated with it. So it proposes a system where the oversight and review would be commensurate with the nature and level of risk associated with the research.

The CHAIRMAN. Your organization is doing important work on accrediting human subject protections at universities on a voluntary basis. Do you believe it would be appropriate to have mandatory accreditation, or voluntary?

Ms. SPEERS. Our organization believes that accreditation should be voluntary, and the reason that it believes that is because it believes that accreditation works best when organizations will make the commitment to change their culture and behavior in the direction that we wish, which in this case is to improve human research protection programs.

That, however, has to be done in coordination with the Federal Government. What I mean by that is it is critically important for the Government to recognize accreditation and for there to be incentives for organizations to seek accreditation, such as a favorable standing with respect to funding, perhaps a reduction in some of the other burdens associated with oversight of their research programs.

It is also important for the Government to recognize accrediting bodies and to monitor the accrediting bodies who in turn are monitoring the institutions.

The CHAIRMAN. My time is up. That was very helpful. Thank you.

Senator Frist.

Senator FRIST. Thank you, Mr. Chairman.

Clearly, our goal needs to be to create and foster an environment that both protects human participants and allows and encourages research in a responsible way. That can be done, and I believe that it is going to take bipartisan legislation coming out of this committee to accomplish that goal given the facts that have been presented today and in the past in terms of the overlap and the confusion and inadequate enforcement of what is on the books today.

I should add that we have taken an important step in this committee by including in the Children's Health Act a provision extending Subpart D of the Common Rule to protect children participating in FDA-regulated research, and Senators DeWine and Dodd have been very involved and were critical to that legislation, and I think our goal needs to be to build in that same vein as we go forward.

The Common Rule is a line of questioning that Senator Kennedy began, and I think it is really critical as we look at the various differences in the regulatory oversight structure, the fact that we hear concerns about the Common Rule being impervious to change. But let me move on to an issue—and Dr. Charles, I will turn to you because you really are on the front line as an active clinical investigator.

The institutional review boards and the issues surrounding them—could you describe your interactions with IRBs in proposing your research and conducting your research. And you mentioned informed patient content, and what I would like you to get to in your comments is any suggestions you might have as to ways that we can improve the training and awareness of clinical investigators in these issues regarding informed consent, human subjects protection, and the effectiveness of the IRB process.

Dr. CHARLES. The first comment I would have about the institutional review boards is that in my own institution, it is the first place that I turn for guidance on procedures for conducting clinical trials and the protection of the people who participate in the clinical trials that I lead.

But I find often that they have conflicting information. They have different rules and regulations that they are trying to follow and that they are trying to get me to follow. Often, the regulatory burden to propose a trial, launch a trial, and then successfully enroll patients and complete the trial can be so high as to create literally a barrier to being able to conduct high quality research.

The one thing that would help that barrier the most is an IRB that effectively educated clinical investigators, helped us become the best physician advocates for the people participating in our trials, and also was there to propose clinical trials, and we design consent forms, and then as we conduct the clinical trial through the whole course of the study.

Senator FRIST. For my colleagues, could you tell us who serves on an IRB at your institution, how long they serve, and what their credentials might be?

Dr. CHARLES. Because the clinical trials have grown so tremendously at Vanderbilt University, we now have two IRBs, often made up of faculty inside the university, people who have experience in health care, participating in clinical trials. They are also, though, members from the community who serve on our clinical trials—medical ethicists, bioethicists, biostatisticians. The complement of people who serve on the committees I would say is terrific. The quality and the expertise is fantastic, and we are fortunate at Vanderbilt to have such high quality IRBs.

I would add, though, that because of the increased regulatory burden, the cost to our institution to perform the oversight of clinical trials is tremendous, and it is not adequately met by the current reimbursements and overheads that are provided by federally-funded research or whether it is industry-sponsored research. The costs are growing exponentially as we try to improve our system of protecting human subjects.

Senator FRIST. And are persons who serve on the IRB compensated directly?

Dr. CHARLES. The members of our IRB are not compensated.

Senator FRIST. And how many clinical trials would there be at, say, Vanderbilt—do you have any idea?

Dr. CHARLES. I do not have the specific numbers—I could certainly provide them to the committee—but it would be in the hundreds. Obviously, at an institution like Vanderbilt and other academic medical centers in our Nation, the number of clinical trials has been growing tremendously over the past decade.

Senator FRIST. And what has your own experience been in informed consent and the regulatory oversight of getting that informed consent?

Dr. CHARLES. It can certainly be confusing when it comes to informed consent. As mentioned earlier by another witness, if you are participating in a trial that is being conducted at many centers, each individual center reviews the consent form, and each individual IRB can change that consent form; so you are conducting the same trial, but patients at different centers might read different consent forms.

Then, from the standpoint of writing consent forms, making sure that you use language that is understood by patients, it is often focused on documenting that you have informed consent. I personally, as an investigator, though, am more concerned that my patient who is considering participating in a trial understands the implications of the research and the trial we are about to launch. In early Parkinson's disease, and an invasive therapy, hopefully supported by the NIH—we will see; we are submitting a grant application—there is actually a study within a study where we are going to test whether the people participating truly have an understanding through the typical informed consent process, and then we are going to conduct an expanded informed consent process.

Senator FRIST. When you go through the informed consent process, and you read through the form, and you explain, typically, what other people will you have in the room in the process itself?

Dr. CHARLES. For trials involving adults——

Senator FRIST. IRB, clinical trial.

Dr. CHARLES. [continuing]. Yes. For trials involving adults, obviously, you are speaking directly with the person who is considering. Often, there is a family member; many times, it may be multiple family members, but hopefully, a spouse or someone directly related to the person if that is possible—that may not be possible. And the study coordinator is often present during the informed consent process, and other health care staff. I am in a teaching institution, so almost everything I do in the clinic, I have a house officer with me, medical students.

Senator FRIST. Is there any requirement for an objective observer to be in the room to make sure that the appropriate things are said? Obviously, when you are one-on-one in a room with people, whether it is financial conflict of interest or just motivation to get this study done, biases can enter into the question. To elevate the level of trust and confidence, is there any requirement for third party ombudsman-type people to be in the room?

Dr. CHARLES. At our institution, obviously, we have a witness or someone who participates in the informed consent process as you go through. Whether you could effectively do that with an ombudsman or someone on the health care staff that would be independent, I think the informed consent process could take place without someone who is not employed by the institution who is completely that insulated. I guess my personal view is that that is not necessary to achieve the informed consent necessary.

Remember that while we have heard today an incredible story, and there are examples in the past, episodes of clinical research that certainly have gone awry, clinical research in our country is a thriving process that creates improved health care for the Nation. I see every day physicians working with patients, I believe that physicians really hold, first and foremost, the principle to do no harm.

Senator FRIST. Dr. Johnson, let me turn to you. All my clinical practice has been in academic research institutions, and I have participated in a number of clinical trials. I always wanted to avoid being on the IRB. I liked doing the clinical studies, liked getting the consent, liked putting the devices in, because you were helping people, and you really were in many ways taking basic science and getting it to patients in a way that you knew in the long term was going to be helpful. But when the call would come about considering serving for 2 years on an IRB and spending up to a day a week not being compensated in a direct way, and drawing me away from research, away from the clinical research that I am interested in, or academic research, it was pretty frightening, and now it is getting more and more because there are more and more clinical trials. I am not sure how we handle that overhead as we go forward, and who is going to be paying for it, who should pay for it, is critically important as we go forward.

What is your experience? Again, you are one step away from these clinical trials in terms of actually getting the consent at Genentech?

Mr. JOHNSON. Yes. So my job is to work with the FDA to write the clinical protocols and make sure that——

Senator FRIST. So you are sort of one step away from where Dr. Charles is. How would you comment on what Dr. Charles has said in terms of being on the very front line? Would you correct or restate anything that he said?

Mr. JOHNSON. No. I think he is exactly accurate. I think one of the biggest concerns that we have in industry is making sure that our physician investigators understand their responsibilities.

Senator FRIST. And what do you think the biggest deficiency in the IRB process is now? You are depending on them doing a good job for you to do a good job. What changes would you make in the IRB process that goes on at the hospital?

Mr. JOHNSON. I think that there should not be just a volunteer process or a sort of delegation process of having people on the IRB. I think there should be some sort of training program so that they truly do understand their responsibilities.

Senator FRIST. And is there today—and my time is up, and I will end with this question—right now, Dr. Frist is recruited to be on the IRB at an institution; I go and sit through the committees, and I am handling probably 50 different studies that I am commenting on, reading the consent form, looking at the ethical, and we are having our discussion. Is there any uniform training, uniform guidelines that are given—I know there are some guidelines—but how am I, Bill Frist, heart surgeon, going to be trained to be an IRB specialist?

Mr. JOHNSON. I think one of the things that people need to be aware of are the GCP guidelines that are through the FDA and the International Committee on Harmonization, which are fairly straightforward in terms of how you are supposed to review informed consents, how you are supposed to make sure that adverse events which occur during the course of the trial are reported to the respective agencies, and to make sure that once those adverse events are reported, the informed consents are, in fact, modified appropriately to reflect the new understanding of the risks involved in the research. I think that is probably the most important thing that the IRBs need to be aware of.

Senator FRIST. Thank you, Mr. Chairman.

The CHAIRMAN. Senator Murray.

OPENING STATEMENT OF SENATOR PATTY MURRAY

Senator MURRAY. Thank you very much, Mr. Chairman, and I especially want to thank you for scheduling this hearing. Obviously, the issue of clinical trials has received a lot of attention in the past year, and there are a lot of clinical trials that are safe, and certainly they provide a lot of life-saving treatments to people with terminal illnesses.

I know the Fred Hutchinson Cancer Research Center in Seattle has gone through some of this in the past year and taken it very seriously, and I commend them. They actually put together a committee to review a number of the allegations and are coming forward with some recommendations that I think will be helpful to our committee as we look at legislative remedies to some of the challenges that clinical trials provide.

I certainly think that in order to restore confidence, we need to look at legislative remedies to ensure patient safety and improved

confidence. So Mr. Chairman, I really appreciate this hearing, and I think it will really help us work toward finding some good solutions.

I want to follow up on Dr. Frist's questions on informed consent, because I think this is a very difficult challenge that we need to face. I know that oftentimes, patients are just demanding a drug even without a clinical trial; obviously, if somebody is in a life-threatening situation, they will do anything, especially if it is your child or your spouse. And informed consent is just a difficult issue to deal with.

I would like to ask Dr. Speers, how can a research institution really ensure that a patient is fully aware of the risks, is comprehending them as they are in a life-threatening situation, and what can we do to ensure that informed consent really is informed consent?

Ms. SPEERS. I think that informed consent is one of the major issues that the commission addressed and struggled with actually over the life of the commission. It addressed informed consent in many of its reports, not just in the oversight report.

But, before I talk about informed consent, I want to back up in the process and say that before one ever gets to the point of an investigator obtaining voluntary informed consent from a prospective research subject, we have to remember that the research is reviewed by an institutional review board. And one of the very important functions of that institutional review board is to examine the risks of the study and the potential benefits of the study, and that board is to look at those risks and potential benefits, and when it approves the study, it is to approve it, if you will, stating that what is being offered to the prospective research subject is a reasonable choice to participate or not participate in the study. So that by the time a potential subject is approached, there has already been review of that research protocol, and it has been determined to be ethically justified to move forward to asking an individual to participate in a study.

The commission was very clear to place emphasis on the informed consent process, not on the informed consent document, where a lot of attention has been placed in the past. That is to say, from the moment a subject is recruited with the announcements, brochures, advertisements about the research to the time that the prospective subject is told about the study, agrees to enroll in it and then participates in that study, that is a process where informed consent occurs during that entire process.

It is very important when the prospective subject is originally approached that the process involve very carefully going over the risks and the potential benefits of the study and the method that will be involved, and the individual is given the opportunity to ask questions, to think about the study, to think about participating in the study.

The more that investigators and IRBs can focus on the process rather than on the consent document, I think we get a lot closer to obtaining voluntary informed consent. But it is an area where I think we need to continue to do more to improve subjects' understanding and comprehension of research.

Senator MURRAY. I appreciate that. The risks and the benefits are a clear part of it. But the other question that I have is how we can help patients better understand any kind of financial link that a researcher or institution may have to the treatment. We are in a market-driven research arena, and I think it is often difficult to separate what is justifiable compensation and what was provided as a way of inducing a bias on the part of the research. So it is a difficult thing. We do not just have Government providing all of the research; we do have private research going on, and it is a market-driven economy, and there are financial links.

How do we make sure—and I would ask both Dr. Speers and Dr. Johnson to respond—that patients understand that financial link?

Ms. SPEERS. The National Bioethics Advisory Commission did consider conflicts of interest, and it looked not only at financial conflicts but at other types of conflicts as well. In looking at conflicts of interest, it pointed out that there were really three groups, if you will, that could have conflicts in the research process. There could be financial conflicts that the institution has; there could be the financial conflicts that an investigator has; and then, the IRB members could have conflicts as well.

With respect to financial conflicts either on the part of the institution or the investigator, NBAC recommended that those types of conflicts need to be disclosed, and they need to be managed by the institutions and felt that it was very important for there to be policies and procedures in place that specifically deal—

Senator MURRAY. And that is not the case now?

Ms. SPEERS. It is not the case now that all institutions have their own policies and procedures in place; that is correct.

NBAC also recommended that there would be disclosure of financial conflicts to the research participants. However, NBAC was also quick to point out that disclosing to participants should not be a substitute for institutions managing those conflicts as well.

Senator MURRAY. Dr. Johnson.

Mr. JOHNSON. I would agree. One of the things that we try to do in industry is make sure that when we do a multi-center study, the level of reimbursement for services provided by the physician investigators is consistent across all sites. This leads to obvious diminution of the perception of conflict of interest.

The second thing is that the FDA now requires that all physician investigators disclose their financial connections with the industry for which they are doing research, and I think this has helped a great deal.

Senator MURRAY. Thank you very much. My time is up, but I do have some other questions that I would like to submit for the record.

[The responses to Senator Murray's questions were not received by press time.]

Senator FRIST. Could I ask a follow-up question?

The CHAIRMAN. Yes, and we will have another round.

Senator FRIST. Just one question on follow-up, because it is still not clear to me. If there is a financial conflict of interest, right now, you have to report it to the institution—you have to do that; is that correct—but according to you, Dr. Speers, the way the institution handles it, there are no guidelines. They are not obligated to tell

the patient, they are not obligated to write anything into the IRB. Is that correct?

Ms. SPEERS. Currently, there is no Federal requirement that an institution that might have a conflict of interest committee, that that committee report its findings to the IRB.

Senator FRIST. If the investigator has a potential conflict of interest, does that have to get reported to the institution, or the IRB?

Ms. SPEERS. There is not a requirement that an investigator disclose his or her conflicts of interest to the IRB.

Senator FRIST. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Just a few final questions, and one for the whole panel. One of the major problems of the current system is failure to monitor ongoing trials. What are the best ways to monitor ongoing trials?

Ms. MATHIAS. I would like to say something about that. You have to have monitors in place to monitor them. A lot of NIH studies are really not being monitored adequately. They seldom if ever send around a monitor. I have been doing an NIH study for 4½ years, and we have never seen a monitor.

Now, if you are doing a pharmaceutical trial, that is different. Because their bottom line is at stake, they send monitors around a lot more frequently. But a lot of the NIH studies which are grant-driven are not adequately being monitored.

Also, I would like to say something about the informed consent process. I feel strongly that there needs to be a third party there to ensure that informed consent is given in such a way that it is not coercive. Particularly in today's environment in a community setting, where many, many subjects are coming from the doctor's own database—they are his patients—and that sets up a conflict of interest between the patient and the doctor and being an investigator and a subject.

So I think there really does need to be a third party there.

The CHAIRMAN. It is amazing to me the number of people who are prepared to volunteer and are willing to be part of these clinical trials.

Ms. MATHIAS. It is often because they are desperate.

The CHAIRMAN. Dr. Speers, would you like to comment on the best way to make sure there is adequate monitoring of the trials?

Ms. SPEERS. Yes. NBAC considered what happens to research after it is initially approved by an IRB and made several recommendations in that area. One was that there should be more guidance provided to IRBs regarding the conduct of the continuing review for research and that continuing reviews really need to be focused on the research that has the greatest risk associated with it.

Right now under the Federal regulations, all research, whether it is minimal risk research or it involves much greater than minimal risk, receives the same type of continuing review. Clearly, we could strengthen the review for riskier research.

The Commission was also concerned about reports of adverse events and how those adverse events are reported and evaluated and recommended that there be a unified system for reporting ad-

verse events, evaluating them, and then reporting back the results of that evaluation to investigators and sponsors and IRBs.

The CHAIRMAN. Dr. Johnson.

Mr. JOHNSON. For most industry-sponsored studies, there are basically three ways that the data and the investigators are monitored. We have standard monitors who go out during the course of the study and check that the data is being accurately recorded and that things are being reported appropriately. Most companies also have separate compliance units which go out and actually audit the sites to really make sure that they are independently reviewed. And then, third, for many of the programs, the FDA will send out auditors to check on investigators.

So currently, I think that industry-sponsored studies are well-protected and well-monitored.

The CHAIRMAN. Dr. Charles.

Dr. CHARLES. Monitoring takes place in many ways. As was mentioned, monitoring takes place locally in my institution right in my division by my own nurse and myself participating in the trials, and then by my IRB, and then, often by the sponsors of the trial that I am conducting.

One thing you mentioned, Senator Kennedy, that is interesting is that it is surprising how many people participate in the clinical trials. The single factor that often plays into a person's decision to participate in a clinical trial is not because they are desperate and hoping for some cure that is not yet proven or not yet there; in fact, when giving informed consent for things that have little risk and sometimes things that have large risk, most of the time, people are interested in participating in a clinical trial because their participation may help others with the same condition in the future, and that is in my opinion and in my experience the most important motivating factor when people are making a decision to participate.

The CHAIRMAN. Dr. Speers, the Common Rule applies to federally-funded regulated research. The Commission recommended applying the standards to all research, whether private or public. What led you to that conclusion?

Ms. SPEERS. It was a basic belief that anyone who participates in research deserves to have their rights and welfare protected. We found when we talked to various groups that there was huge support for including all research under a set of Federal regulations, that much research is included either because it is federally-funded or because it is regulated by the Food and Drug Administration.

The CHAIRMAN. Your current program does accreditation on a voluntary basis, but the Bioethics Commission recommended that all doctors and review boards be accredited. Isn't that a call for required accreditation? You have that here in your recommendations.

Ms. SPEERS. Yes, I do, yes. The National Bioethics Advisory Commission and AAHRPP, the organization I now work for, I believe do share a common goal, and that common goal is that we would like to see all individuals certified, and we would like to see all institutions accredited. The question is how best to obtain that goal. AAHRPP believes the best way to obtain it is through voluntary accreditations where institutions seek it when they have made the commitment to do so.

The NBAC report in the text that accompanies that recommendation says that as we are moving closer to certification and accreditation, there should be some flexibility initially to test different methods and procedures with respect to accreditation and noted that highly successful accreditation programs have tended to be voluntary.

The CHAIRMAN. I appears from all the testimony that we have lots of regulations, but not necessarily the right regulations, and we need to make sure that structures appropriate for modern clinical trials truly protect patients. Do you have views about whether that ought to be an independent agency or where it ought to be located? That is a bureaucratic kind of question, but I would be interested if you have a view and reasons for it—should it be in HHS or FDA—if you have a view, I would be interested in whatever reasons you might have.

Ms. SPEERS. The National Bioethics Advisory Commission did have a view on it, and they spent quite a bit of time deliberating over the placement of that oversight office, and they strongly believed that the oversight office should exist independent of any Federal agency; that is, it should exist outside of any Federal agency.

The reasons for that thinking were that they wanted the office to have high visibility to really show the Government's commitment to protecting human research subjects and for there to be a central focal point.

They were also concerned that if such an office were placed within a Federal department that that could potentially create a conflict of interest between the mission of the independent office and the mission of that department, meaning that the department is likely to have a mission to promote and enhance research, which at times could be in conflict with the mission of the independent office, which would be to protect human research participants.

The CHAIRMAN. Do others have a view?

Dr. CHARLES. Certainly in HHS, where in particular I guess would not be so important to me as an investigator; more important would be that it was consistent and applied across all Federal agencies when human subjects are involved.

Ms. MATHIAS. I would like to say something about that, too. Not only does it matter if they are independent, but we must give the regulators the tools necessary to do enforcement. I know that OHRP, Greg Koski, has asked that they be able to fine individual investigators up to \$250,000 if they are noncompliant. That is essential. We must give them tools for enforcement.

The CHAIRMAN. Thank you.

Senator Frist.

Senator FRIST. Thank you, Mr. Chairman.

We have touched on a number of issues, and I appreciate everybody's comments. One area that we have not explored quite as deeply but we have in past hearings is the adverse event reporting in clinical trials. As I mentioned in my opening statement, compared to where we were a year ago or even 2 years ago, I feel that progress is being made. I think that legislation is going to be required. We have to address these issues of what is mandatory,

what is voluntary, and that is where a lot of these questions are coming from.

Just in March, the NIH offered a \$28 million program to enhance human subjects oversight. And again, when you look through those announcements and the way it was presented and what applicants have to detail, whether it is tracking systems for monitoring, infrastructure technology development for tracking human subject protocols, facilitate IRB activities, coordinate the activities of IRBs—again, a lot of the individual institutions and programs like NIH are working very hard. I do believe we are going to need some greater coordination throughout Government for this and look forward to working to do that.

On adverse events and reporting, Dr. Johnson, because you are receiving them, and Dr. Charles, you are again on the front line, how would you summarize where we are today? I can tell you that a year-and-a-half ago in a hearing, we spent probably 3 or 4 hours talking about how poorly adverse events are recorded, interpreted, and then shared, and ending up with enforcement. Where are we today?

Mr. JOHNSON. Well, again, I think that industry is reasonably well-regulated on this. We do understand our responsibilities. Quite frankly, the worst thing that can happen to me when I am conducting a clinical trial is that some unexpected adverse event occurs and that I don't tell everybody about it. First, I feel bad for the patients, obviously; but second, we need to let everybody else to know to look for these things so that we can act early to prevent bad things happening. And I think we do have in industry mechanisms in place to deal with that effectively. We are also very closely regulated by the FDA on this one. We sit around and carefully review reports of adverse events, determine whether they fit into various categories of expedited reporting or routine reporting. We make sure that the informed consents are updated appropriately and that we have reviewed those with the institutional review board at each investigative site.

So I think that within industry, the process is pretty well-established, and people are pretty well-educated. I think education, possibly, with independent investigators is probably the most important issue that you would like to address.

Senator FRIST. And you report that to the FDA?

Mr. JOHNSON. Yes.

Senator FRIST. To anyone else?

Mr. JOHNSON. I report it to all of our investigators whether they are active—so if they participated in previous studies of the same compound, we report it to all of those investigators. And certainly for any active trials, the investigators are required to send that letter on to their IRBs.

Senator FRIST. Do you have any suggestions for the Government entities to whom you report adverse events? Do they handle the data correctly, get back with you, give appropriate oversight?

Mr. JOHNSON. Oh, yes, absolutely. Usually, when we get an expedited report, we will actually telephone the medical reviewer at the FDA and discuss the case with them.

Senator FRIST. Dr. Charles, do you have any comment on adverse events?

Dr. CHARLES. Certainly in receiving adverse events and recording them, it is a critical part of the clinical trial that you are conducting. From the standpoint of an investigator, I am conducting a clinical trial at this time in a biologic that is injected. The company, the corporate sponsor of the trial, is conducting many trials with this drug, and I am receiving adverse event reports for this agent well outside my clinical trial. All of those reports come to me, and I review them, assess the impact that they might have in my clinical trial—do I need to change my consent form—but in addition to that, I have to inform my local IRB, and they make the same assessment with me.

Again, as a clinical investigator, I look to my institutional review board to guide me on how to report things that are serious adverse events and how to report adverse events that are not as serious.

Senator FRIST. On the accreditation, it is still unclear to me. Are we accrediting institutional review boards or programs? Dr. Speers, I guess you would say programs, or is it an institution; is it Vanderbilt University, or is it one of the two IRBs at Vanderbilt University that you would accredit voluntarily or others mandatorily?

Ms. SPEERS. We would accredit institutions, and what we are accrediting within institutions is what we call their human research protection programs that include their IRBs. The reason for doing that is that the responsibility for protecting human research participants is a shared responsibility. It is not the responsibility solely of the IRB. It is an institutional responsibility, and it is an investigator responsibility.

So our accreditation program looks at all of those responsibilities and has standards that they have to meet in all of those categories of responsibility.

Senator FRIST. And outside of, say, academic health centers where so many of the clinical trials are, is that easy to do? Again, we have this huge spectrum of research where you would like to see oversight over both the private and the public. Paint the picture of some research that is done out in the middle of nowhere where nobody knows the research is going on—which is happening, obviously.

Ms. SPEERS. Yes. Our organization accredits all types of research institutions. That is to say, it is not a program that is geared specifically to the universities. We will accredit eligible organizations that could include independent review boards, community hospitals, Government agencies, pharmaceutical companies that conduct their own research, contract research organizations—the full array of organizations that are involved in the research process.

Senator FRIST. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Just finally, Dr. Speers, we have heard what is happening in industry, but of course, there is an enormous amount of research that is being done outside, and we obviously want to make sure that those human subjects are going to be protected. How important do you think it is that we make the changes which are necessary and make them now?

Ms. SPEERS. I think that it is really very important to make changes to the oversight system. I think that some of the basic problems that have been discussed here today—we have talked, for

example, about the system being confusing to investigators or to IRBs, that there is some research that is not covered by the system, that IRBs are overburdened, and in part they are overburdened because the current set of regulations does not distinguish very well between the less risky research and the more risky research.

I think that in order to improve the system, to really get to the level that we all want with protection programs, there are some basic changes that need to be made to the system, particularly a single set of regulations, a single office that can then oversee the oversight system. I think that those are critical to bringing about the kinds of changes that we want to see in the system.

The CHAIRMAN. Ms. Mathias.

Ms. MATHIAS. I would like to add to that that in everyday practice, it is confusing. The adverse event reporting is confusing. A lot of investigators do not understand it. Also, to be quite honest, I wish we could clone Dr. Charles, because it sounds to me like he is——

The CHAIRMAN. We have to be careful on that subject now. We do not want to get Senator Frist all worked up. [Laughter.]

Senator FRIST. No, we are both against that kind of cloning.

The CHAIRMAN. You are right on that.

Ms. MATHIAS. But he is intricately involved with his clinical research. I have found in my own practice that many, many physicians leave most of the work up to the study coordinators, because they are too busy with their day-to-day practice, and it is the study coordinators who are actually judging the adverse events and then pass it by the investigators.

I can promise you that adverse event reporting is still an area that needs much work. They are not being collected adequately; they are not being reported adequately, and once they are given to the IRBs, the IRBs have a tremendous problem with what to do with them because they are not given all the information they need from the sponsors. They do not know, when you report an adverse event to an IRB, if they are on a placebo or if they are on the active agent. So it makes it very difficult for an IRB to be able to use that information and actually review it to where they have something that is valid to deal with.

So those are still problems that are inherent in the system that have not been corrected.

The CHAIRMAN. And that you believe need change; is that right?

Ms. MATHIAS. Definitely.

The CHAIRMAN. I do not know if you want to make any comment, Dr. Charles.

Dr. CHARLES. For the record, my wife and my chairman would both like to clone me, but I am firmly against that. [Laughter.]

The CHAIRMAN. Well, this has been enormously informative, and it has been distressing in the sense of some of the loopholes that are still out there and the overlap of different rules and regulations which are bringing in efficiencies and that clearly have to be recognized. But I think there is certainly a sense that we have to try to take what has been suggested here today and other testimony and try to see if we can upgrade this system to help us protect human subjects and also ensure that the opportunities for these

new breakthroughs that will enhance health care for so many people will continue. That is a very important responsibility for our committee, and we are going to need a lot of help in being able to do it, and we are going to all work together.

We will leave the record open for 2 weeks if there are other questions to be directed toward you. We thank you all very, very much for your appearance here today.

[Additional material follows:]

ADDITIONAL MATERIALS

PREPARED STATEMENT OF MYRON GENEL, M.D.

Good morning. I am Myron Genel, M.D., a professor of pediatrics and associate dean at Yale University School of Medicine where I have directed the medical school's Office of Government and Community Affairs. Currently I am Chair of the Advisory Committee of Yale's Children's Clinical Research Center, having formerly served as its program director for 16 years and Chief of the Section of Pediatric Endocrinology, where I remain active clinically. Relevant to these hearings, I have been a member of the Yale Human Investigation Committee, the medical school's institutional review board (IRB), for 30 years and am a member of the Children's Workgroup established last year by the National Human Research Protections Advisory Committee (NHRPAC). I am also a member of the Institute of Medicine's Clinical Research Roundtable and past Chair of the American Medical Association's Council on Scientific Affairs.

I am pleased to be here this morning representing the American Academy of Pediatrics and its 55,000 pediatricians and pediatric subspecialists who have committed themselves to helping improve the health of children. In addition, I am representing the Pediatric Academic Societies, comprised of the American Pediatric Society, the Ambulatory Pediatric Association, the Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research. These organizations consist of pediatric researchers, full time academic and clinical faculty responsible for the training of pediatricians, and the leadership of medical school pediatric departments.

These are extraordinary times for advancing the health and well-being of all members of society, but especially for children. As pediatricians, we are pleased that significant strides have been made over the last several years to include infants, children and adolescents in clinical research. In order for children to benefit from the wealth of research of how humans learn, grow, and develop and how science can address disease and illness the pediatric population must participate in those research opportunities.

But with this awareness and commitment comes the responsibility that we—pediatricians, politicians, parents, researchers, Government, academia and industry—must be ever vigilant to ensure that the pediatric population is fully protected from inappropriate or unnecessary risk in clinical research.

Congress has provided great leadership in moving pediatric research forward. The success of the pediatric studies provision within the Food and Drug Administration Modernization Act of 1997 (FDAMA) has increased the number of children participating in clinical research. AAP is also pleased with the enactment of the Best Pharmaceuticals for Children Act (P.L. 107-109), which reauthorizes the pediatric studies provision and enhances therapeutic research for children. This law is a result of legislation championed by Senators Christopher Dodd (D-CT) and Mike DeWine (R-OH) and Representatives Anna Eshoo (D-CA) and Jim Greenwood (R-PA).

Especially significant was the October 2000 enactment of the Children's Health Act (P.L. 106-310), which includes research and program creation and expansion in many areas of childhood diseases. Three components of the Children's Health Act are of particular interest in light of today's hearing: (1) the establishment of the pediatric research initiative at the National Institutes of Health (NIH) which will support research that is directly related to children's health; (2) the provision to evaluate the existing Federal regulations that protect children (subpart D of part 46 of title 45, Code of Federal Regulations) and (3) the requirement that all research involving children that is conducted, supported, or regulated by HHS be in compliance with Subpart D.

AAP, joined by the pediatric academic societies, was pleased to provide comments to Dr. Greg Koski, Director of the Office of Human Research Protections (OHRP) of the U.S. Department of Health and Human Services (DHHS) on evaluation of existing subpart D regulations. AAP and the pediatric academic societies agree with the recommendations made by OHRP in its report "Protections for Children in Research: A Report to Congress in Accord with Section 1003 of P.L. 106-310, Children's Health Act of 2000." As a member of the National Human Research Protections Advisory Committee's (NHRPAC) children's workgroup, I was pleased to play a role in the development of this report. The report recommends that subpart D should not be modified at this time. In addition, the report states that HHS should provide detailed guidance relevant to the complex issues inherent in both the conduct of research involving children and the interpretation of the provisions of the regulations under subpart D to all parties engaged in the conduct and oversight of

research involving children. AAP and the pediatric academic societies look forward to working closely with NHRPAC and OHRP on these recommendations in the future.

In July 2001, the AAP also provided comments to the Food and Drug Administration on the Interim Rule that was issued on April 24, 2001 in compliance with the Children's Health Act provision requiring research protections for children throughout HHS. AAP strongly supports the FDA's adoption of the safeguards provided in subpart D. However, we provided several specific comments [attached].

Children in Clinical Research: To begin with, the conduct of research in children carries with it the same ethical obligations as research in adults. However, children comprise an especially vulnerable population and must be provided added protection against violation of their individual rights and exposure to undue risk. This situation imposes special considerations when inviting participation in studies, assessing risks and benefits, and ensuring equitable participation and benefits in clinical research. There are three general principles of pediatric research that have been the tenets of AAP policy:

1. Children need to be involved in research so that medical advances can continue to be made and so that children can enjoy equal access to beneficial medical treatments.
2. Adequate protection needs to be in place to protect the rights of the children who are actually participating in research.
3. Local institutional review boards (IRBs) are capable of protecting the rights of children, but it is imperative that these IRBs have proper pediatric expertise and adequate institutional support.

PARTNERS IN RESEARCH

There are multiple partners in the conduct of sound research. No one individual or institution can stand alone in creating an environment that ensures scientific rigor and protections for pediatric patients.

Investigators: The investigator's competence and ethical conduct are the most important safeguards for the protection of the child. The investigator must understand the developmental and ethical issues involved in research with children. In addition, they must be able to recognize adverse events that occur in children and have sufficient pediatric expertise to ensure safety of children in pediatric research.

The investigator should make every attempt to appreciate the feelings of all parties concerned, and attempt to understand the fears and concerns of the children. The investigator should be an effective communicator to the subjects and their parents in order to decrease fears about the clinical protocol and its procedures. These considerations are important, because children and their parents may be unable or unwilling to voluntarily communicate their feelings and fears. The investigator should endeavor to understand the attitudes and motivations of the parent and other individuals qualified to act on the child's behalf.

Institutional review boards: The primary responsibility of the institutional review board (IRB) is to protect the rights of the research subject. This includes responsibility for interpreting the Federal guidelines and determining whether or not each study is designed ethically in compliance with the Federal guidelines, local and State law, and the local IRB directives. Any individual or institution under whose auspices clinical research is conducted must assure that the research protocol is reviewed by an appropriately constituted IRB.

The AAP believes that local IRBs are capable of protecting the rights of children involved in research. Flexibility in the current Federal regulations allows for local interpretation and definition, and the regulations recognize that individual IRBs can adopt strict guidelines for assessing acceptable risk in order to protect children. It is however, imperative that IRBs have at a minimum one member present when research involving children is reviewed who has appropriate expertise in pediatric medical care. Consistent with the Food and Drug Administration's draft Guidance on Clinical Investigations of Medicinal Products in the Pediatric Population (ICH E-11) "there should be IRB members or experts consulted by the IRB who are knowledgeable in pediatric ethical, clinical, and psychosocial issues."

In addition, the IRB should establish a mechanism to assure that no child is enrolled in more studies than is consistent with his or her welfare. There may be reasons to enroll the same child in more than one study simultaneously. In most instances this does not jeopardize the child's welfare or safety, but in some situations the child's participation in more than one study may be detrimental to the child or may confound the scientific validity of the studies.

Parents/Guardians: The key role of the parent or guardian is to act in the interest of the child. An essential element is to give his or her permission before the minor

is approached for his or her assent. For research that does not offer the prospect of direct benefit and has greater than minimal risk and for research requiring the approval of the DHHS Secretary, both parents or guardian/s must give their permission if feasible.

Ethical Considerations: Areas of concern in designing and performing pediatric research include determination of benefits and risks, obtaining informed parental permission and child assent to participate, protection for vulnerable populations, and specific aspects of research design.

Determination of Benefits and Risks: The AAP believes that benefits of research should be construed broadly and should be considered carefully by local IRBs. The AAP further supports the clear separation of benefits that directly improve an individual subject's well-being and that provide generalizable knowledge regarding that child's condition or in childhood health and disease more generally. The evaluation of direct benefits should primarily take into account treatment for the subject's own benefit. Even when this is not the primary purpose of a study, the child may directly benefit from the knowledge gained from the study itself or by being in the active arm of a placebo-controlled trial, where appropriate. The understanding by the child that he or she has contributed to the study of a childhood disease or the biology of children should be considered secondarily.

The risks to the child should also be evaluated in the broadest context. These incorporate known and predictable effects of the treatment and procedures including discomfort, inconvenience, pain, fright, separation from parents and familiar surroundings, effects on growth and development, and the size or volume of biologic samples.

Remuneration for Participation in Research: An area that has received considerable attention is whether payment (financial or otherwise) may be provided to a child or his or her parent or guardian for the participation of the child in research, and if so, the amount and type given.

AAP believes that it is in accord with the traditions and ethics of society to pay people to participate and cooperate in activities that benefit others. However, serious ethical questions can arise when payment is offered to adults acting on behalf of minors in return for allowing minors to participate as research subjects. The AAP believes parents should not profit from placing their child in research and thus remuneration should not be beyond out-of-pocket expenses and a token gesture of appreciation for participation. If remuneration is to be provided to the child, it is best if it is not discussed before the study's completion. This will help assure that the remuneration is not part of the reasons that a child volunteered or is volunteered for a study.

The study also may make funds and facilities available to reimburse the child (or the family) for any direct or indirect costs incurred because of the child's involvement in the study and a waiver of medical costs associated with treatment under a research study may be permitted in certain circumstances. However, the investigators and the IRB must be certain that the compensation offered is fair and does not become an inducement for the participation of a child subject and the IRB should carefully review any proposed remuneration to be assured that the possibility for coercion has been avoided.

Permission/Assent/Consent: In pediatric studies, the investigator is required to obtain written permission from the parents and, when applicable, assent from the child before the study except when specifically exempted by the IRB. In certain cases, such as when emancipated or mature minors are studied, consent from the adolescent is necessary and permission from the parents may be waived by the IRB.

Assent of the Child: Assent should be obtained from children who are capable of assent. The purpose, risks, and benefits of a study should be explained to the subjects at a level appropriate to their intellectual age. In addition, parental permission is required before the child's participation in a research protocol. Assent must be an active affirmation by the research subject and should usually be obtained from any child with an intellectual age of 7 years or more. Assent may be waived in therapeutic research studies in which, in the opinions of the IRB, the research holds out a prospect of direct benefit that is important to the child's health or well-being and is not available outside of the research.

Quality Assurance and Accreditation: The task of ensuring that ethical principles indeed are being adhered to when children participate in research is formidable. The Office for Human Research Protections clearly has expanded its reach over the past year by initiatives to increase the number of institutions filing Federal-wide assurances of research protections. Moreover, the building movement toward voluntary accreditation of human protections programs has the potential to further improve the system.

At the same time, the accreditation standards must not become overly idealistic nor should they focus excessively on administrative paperwork within IRBs and human protections programs. Now is the time to assure this new accrediting body focuses on the meaningful issues most important to protecting human subjects and not inconsequential details. Of highest priority should be investigator/patient communication or relationships. We encourage the Government to examine a variety of approaches to quality assurance.

We applaud the recent grant money made available by NIH within the "Human Subjects Research Enhancements Program" to improve human protections activities. This is a good example of innovative approaches to encourage ethical research. Another potentially productive, but underutilized, avenue to assess quality assurance is patient outcomes and parent/patient post-study feedback in research studies. Comparisons of non-randomized control groups have indicated that children involved in research, even those assigned to non-treatment arms of studies, have better outcomes than those not involved at all in the research. Better collection of data showing the direct benefits of research for patients need to be collected to demonstrate that parents and children are satisfied that they are respected and cared for ethically within research studies and that they are content with their participation decisions.

CONCLUSION

While AAP is pleased with progress being made to include more children in research, we are disheartened with a recent proposal by the Administration to potentially suspend all or part of the 1998 Pediatric Rule. Both Congress and the Executive Branch have been proactive in moving children's health to a more visible position within the research community. We are beginning to get more and better scientifically-valid and ethically appropriate information related to children's health. Now is not the time to consider delaying or rolling back the advances being made in therapeutics for children. AAP strongly urges Congress to continue to encourage and support efforts to advance the health and well-being of children through research initiatives.

A concrete example of the advances made for children's health is the increased number children in clinical drug studies and the prospect of more children participating in this research. This is testimony to the success of pediatric studies provision in FDAMA and now the Best Pharmaceuticals for Children Act. Through these important clinical studies, information is generated and then disseminated for use by pediatricians and other health professionals. What is the alternative to including children in these well-controlled, scientifically-valid pediatric studies? Having hundreds of thousands of children taking medications in office settings or at home that have not been properly studied. Subjecting children to daily uncontrolled, unregulated, and unreported practices versus including a significantly smaller number of children (thousands vs. hundreds of thousands) in controlled clinical research studies is a much-preferred alternative.

The pediatric community believes we must be continually diligent to ensure that children are protected in clinical trials but also that children are afforded every opportunity to participate in essential clinical research. The pediatric community, as represented by the AAP and the pediatric academic and research societies, is confident that a framework exists to provide these protections. We must all work together to ensure that all aspects of this system are working in harmony to achieve these common goals.

RECOMMENDATIONS

AAP and the pediatric academic societies believe that efforts to review and modify human research protections for the entire pediatric population are extremely valuable. AAP and the pediatric academic societies would propose the following recommendations:

While the regulations under subpart D of part 46 of title 45, Code of Federal Regulations are sound, there is unacceptable variability in the interpretation of the regulations and the expertise of the IRBs and investigators. Clear guidance from the Federal Government can assist in this unjustified variability of the interpretations of the regulations.

With the Office of Human Research Protections (OHRP), ensure there is staff with expertise in pediatrics designated to address human subject research protection issues, both ethical and clinical, specifically related to pediatric populations.

Formalize an independent pediatric workgroup within OHRP. The purpose of this pediatric workgroup would be to inform, advise, and participate in activities and

recommendations developed by OHRP and the National Research Protections Advisory Committee (NHRPAC).

The AAP is pleased that the Best Pharmaceuticals for Children Act includes a provision that instructs the Secretary of HHS to contract with the Institute of Medicine to conduct a review of Federal regulations, reports and evidence-based research involving children. We note that this report is due by January 2004 and would encourage the Secretary of HHS to ensure that the IOM begins developing their review and recommendations in the immediate future.

FDA should adopt a modified version of section 46.408(c) subpart D pertaining to waivers of informed consent for adolescents. FDA decision not to adopt this provision fails to appreciate that there are limited circumstances when the rights of participants would be better protected by requiring adolescent assent in combination with appropriate alternative protections rather than guardian consent.

As a component of ensuring adequate, well-controlled, ethically appropriate and scientifically valid research, the FDA should consider making public written requests issued to pharmaceutical companies under the Best Pharmaceuticals for Children Act (P.L. 107-109). Such a requirement would help assure through public discussion the appropriate protections of children enrolled in pharmaceutical research."

The 1998 Pediatric Rule established a therapeutic foundation for children and works in conjunction with the Best Pharmaceuticals for Children Act. To ensure that safe and effective therapies are available for infants, children and adolescents, Congress should legislatively codify the 1998 Pediatric Rule.

I appreciate the opportunity to present the thoughts and recommendations of the American Academy of Pediatrics and the pediatric academic societies. I would be pleased to answer any questions you may have.

PREPARED STATEMENT OF ROBERT P. KELCH, M.D.

Mr. Chairman and members of the subcommittee, I am Bob Kelch, M.D., Dean of the University of Iowa's Roy J. and Lucille A. Carver College of Medicine. I also serve as the Chair of the Advisory Panel on Research for the Association of American Medical Colleges (AAMC). The AAMC represents the 125 accredited U.S. medical schools; the 16 accredited Canadian medical schools; some 400 major teaching hospitals, including 74 Veterans Administration medical centers; more than 105,000 faculty in 98 academic and scientific societies; and the Nation's 66,000 medical students and 97,000 resident physicians. Our member institutions conduct a very large share of the biomedical and behavioral research performed in this country, and we have been the source of many of the dramatic breakthroughs that have revolutionized biology and are transforming medicine. My testimony today will focus on how the AAMC, on behalf of our members, has undertaken significant new initiatives aimed at strengthening the protection of the many thousands of human patients and volunteers who participate in medical research each year.

The AAMC commends the subcommittee for convening this hearing to explore the issues surrounding the protection of human research participants. We recognize that academic medicine and the American public have forged a special relationship rooted in trust that is nowhere more evident—or more fragile—than in clinical research involving human participants. We are troubled by recent reports of lapses in the oversight of clinical research in some of our most prestigious members, reports that threaten public confidence in our Nation's system for protecting research participants. And we are disturbed by allegations that the financial interests of faculty investigators or their institutions may have compromised their independence and credibility, and threatened the welfare of research participants as well as scientific integrity.

AAMC and its members are vitally concerned for the safety and well-being of the patients and healthy individuals who participate in our research programs. We believe that their protection can be most reliably achieved and effectively sustained in settings that place a high priority on, and devote significant attention to, research ethics, as well as compliance with legal and regulatory requirements. We agree with OHRP Director, Dr. Greg Koski, that the most effective programs of protection of human research participants will occur in institutions that go beyond compliance to foster "a culture of conscience and responsibility" that lodges not just in institutional review boards (IRBs), but in every principal investigator and all of those who engage in clinical research.

To assist our members to create and maintain such a desired culture of conscience and responsibility, and to achieve uniformly high standards of human research protections across the entire community of academic medicine, we have organized na-

tional research compliance conferences, and have worked jointly with the organization Public Responsibility in Medicine and Research (PRIM&R), to sponsor focused regional educational programs for institutional review board members and staff, faculty who conduct clinical research, and institutional officials responsible for its oversight in our member institutions. All of these efforts have been enthusiastically received and over-subscribed. A year ago the AAMC created a compliance website (www.aamc.org/research/dbr/compliance/startcom.htm) to publicize and make accessible the most promising initiatives developed by our members to address the education and credentialing of clinical investigators. A number of attractive approaches were already in development by our members well before October 2000, when the NIH made such educational programs mandatory for its awardees. The credentialing of clinical investigators, an approach initiated by the University of Rochester Medical Center, is becoming widespread and will soon be a requirement. Visitors to the AAMC compliance website can locate a rich set of information related to Federal regulations, model policies and procedures, and available educational resources.

During the remainder of my testimony, I will emphasize two major new initiatives in which the AAMC is heavily engaged: initiatives designed to ensure the safety and well-being of the patients and healthy individuals who volunteer to participate in our research programs. First, we have worked to establish a system of voluntary accreditation of institutional programs of human research participant protections; second, we have developed and published our first report, including detailed guidelines to address the concerns that have been raised about financial conflicts of interests in clinical research.

ACCREDITATION

Despite the existence for more than 25 years of an evolving code of Federal regulations (since 1991 commonly dubbed “the Common Rule”) and policies to protect the rights and welfare of human research participants, there has been increasing concern in recent years that the system for protecting these participants needs improvement. These concerns were dramatically underscored by the recent wave of Federal suspensions of research at various institutions around the country, which indicated to many that systemic improvements in human research protection programs are necessary. While acknowledging that researchers and IRB members are generally adhering to the Federal requirements for protecting human research participants, the Inspector General of the Department of Health and Human Services observed that the national system for protecting research subjects is currently under strain and facing increasing pressure in a rapidly changing research environment.

IRBs have a significant number of weighty responsibilities. Under the terms of the assurances their institutions provide to Federal funding agencies, IRBs must make certain that the research they oversee is conducted in accordance with Federal policies and all applicable State and Federal laws. To assure that the risks to human participants are minimized, IRBs must assess these risks in hundreds or even thousands of research protocols, while meeting exacting procedural requirements and maintaining detailed records. Moreover, even as the complexity of clinical research and the volume of research protocols are increasing, IRBs must respond to an ever-expanding array of Federal and State requirements that, in the aggregate, have become procedurally onerous, and, some argue, distracting.

Given that within the academic community IRB members are almost always volunteers with major responsibilities in teaching, research, and often, patient care, it is not surprising that they are finding it difficult to accept progressively increasing new burdens of oversight, or finding the time and resources to undertake periodic self-assessment. The AAMC agrees with Dr. Koski that responsibility for ensuring the well-being of human research participants in this rapidly changing environment of clinical research, can no longer be considered primarily to rest on IRBs, but must become the duty of all who are engaged in the enterprise. The British code of medical ethics speaks of a solemn “duty of care” that rests on every physician; the AAMC suggests that same ethical “duty of care” should rest on every physician-investigator who conducts research on human participants.

Universities, medical schools, and teaching hospitals must work to instill across their campuses, in all who engage in human participant research, a new sense of shared obligation and a new culture of individual responsibility. The AAMC believes, based on its long experience with many different kinds of academic accreditation programs, that establishing a mechanism of voluntary accreditation of human research protection programs would be very helpful to our members, as well as the broader academic community, in accomplishing the changes in faculty attitude and institutional culture that are necessary. The idea of creating such an accreditation

mechanism had been debated within PRIM&R circles for several years. In May 1999 PRIM&R announced that it would develop a program of accreditation for human research protection programs, which it dubbed AAHRPP (Association for the Accreditation of Human Research Protection Programs), and formed a committee to begin to draft accreditation standards. Since that time, as I will describe, the AAMC has partnered with PRIM&R to bring this concept into existence in a way that is consonant with our traditional and uniquely American model of voluntary, peer-driven, educationally focused accreditation of academic institutions and their components.

The accreditation model, while necessarily conforming to all applicable statutory and regulatory requirements, is importantly different from the regulatory model, common in other countries, which focuses purely upon regulatory compliance. Accreditation fosters a process of self-examination and a culture of self-improvement that is stimulated and nurtured by the accreditation process itself. AAMC shares with PRIM&R the belief that such an accreditation process for human subjects protection programs should combine objective, outcome-oriented performance standards with on-site reviews involving collegial dialogue and education. An approach that is collaborative yet based upon clearly-defined standards will encourage institutions to strive for ever higher levels of performance beyond the threshold of compliance. The ultimate objective of accreditation will be to foster a commitment to continuing quality improvement within each institution's system for the protection of human research participants.

The AAMC conceived of AAHRPP as a non-profit member corporation, in which the members would be the large Washington-based associations representing America's universities (Association of American Universities and National Association of State Universities and Land-Grant Colleges), medical schools and teaching hospitals (AAMC), biomedical scientists (Federation of American Societies for Experimental Biology), behavioral and social scientists (Consortium of Social Science Associations), patient advocacy organizations (National Health Council), and IRB experts (the Boston based PRIM&R). AAMC took the lead in forging this alliance, securing funding, and bringing AAHRPP into existence; AAHRPP was incorporated in the State of Maryland on April 23, 2001. AAHRPP's mission is to provide a process of voluntary, peer-driven, educationally-focused accreditation and continuing quality improvement for academic institutions and other organizations concerned with research involving human participants. AAHRPP's goal is to create and administer a highly respected program of accreditation that is viewed by the larger research enterprise, the Federal Government, and the public as safeguarding and improving the protection of human research participants. AAHRPP is now operational and a full slate of site visits is anticipated to be performed this year.

AAHRPP is governed by a 21 member board of directors that includes 5 public representatives and has full authority over the organization and its accreditation programs and activities. The founding members serve in a trustee role, with strictly circumscribed fiduciary responsibilities; the members will have no role whatever in the operations of AAHRPP or its decision-making processes. The executive director of AAHRPP is Marjorie Speers, Ph.D. and the president is David Skorton, M.D., from the University of Iowa.

The AAMC is very pleased to have been able to play a major role in the creation of AAHRPP and is prepared to continue to do whatever it may be asked to ensure its success. We believe that AAHRPP will contribute in important ways to the change in culture of human participant research, which Dr. Koski has repeatedly called for, and to which our members and we unequivocally subscribe.

CONFLICTS OF INTEREST

Following the reports of several tragic events that occurred in gene transfer experiments in which both faculty and their sponsoring institutions were perceived to have significant financial interests, the Administration, the Congress, and the media began to question the sufficiency of current Federal conflict-of-interest guidelines, the credibility of institutional conflict-of-interest policies, and the dependability of academic institutions in complying with their own policies. Driving this concern was the fear that financial conflicts of interest may jeopardize the safety of research participants and the integrity of research data. This topic had last captured public attention in the 1980s, when congressional hearings cast a harsh light on several instances in which financial conflicts of interest seemed linked to scientific misconduct in clinical research.

More than a decade ago, the AAMC developed and published guidelines to aid its membership in addressing faculty conflicts of interest in research. These guidelines were a necessary response to the emerging paradigm of university/industry collaboration spurred by the Bayh-Dole Act, which in 1980 gave universities title to inven-

tions arising from federally-sponsored research. Bayh-Dole created fertile ground for nurturing the transfer of basic research findings to the developers of beneficial products, but also gave rise to new incentives for investigators and their institutions to pursue financial interests in the course of scientific research.

Although the AAMC guidelines have served as a useful model for conflict of interest policies developed by individual medical schools and teaching hospitals, recent studies have indicated that across the academic community, approaches to identifying and managing individual financial conflicts of interest vary widely. Of particular concern is the absence of consensus regarding the proper management of related financial interests in clinical research that involves human participants. Moreover, neither the AAMC guidelines nor most institutional policies address the conflicts that may arise from the financial interests of the institutions themselves, which have increased substantially in the past decade from both royalty streams and equity holdings. Although conflicts of interest are ubiquitous and inevitable in academic life, as they are in all professions, the existence of related financial interests of either individual investigators or their institutions in research involving human participants raises special concerns. Yet, such interests have become particularly widespread in academic medicine, which has spawned a flourishing biotechnology industry, generated an insatiable public appetite and impatience for ever more wondrous treatments, and contributed importantly to the intense public and political interest in universities as sources of regional economic prosperity.

Our collective experience with the increasingly commercial nature of academic research and our obligation to be responsible compel a thorough reexamination of how the academic medical community manages financial interests in research involving human participants. The AAMC believes it imperative that our community take the initiative in reassuring the public and policymakers that neither institutional nor faculty financial interests will be permitted to compromise the safety of human participants or the integrity of biomedical research. AAMC President Jordan Cohen, M.D., made financial conflicts of interest the theme of his address at the AAMC 2000 Annual Meeting, where he announced the formation of a high level Task Force on Financial Conflicts of Interest in Clinical Research. The association chose to focus the efforts of the task force upon financial conflicts of interest involving human participants, in part because we perceive an urgent need to rethink and revise our guidance in this area, and in part to complement the activities of an AAU Task Force on the Responsible Conduct of Research, which examined some of these same issues from the campus-wide perspective of university presidents. In composing our task force and developing its charge, we were particularly sensitive to the special relationship of trust that academic medicine enjoys with the American public. The work of the task force was guided by our commitment to sustain that trust in the context of the new, extraordinarily promising, and far more entrepreneurial environment in which we now conduct research.

Chaired by William Danforth, M.D., chancellor emeritus of Washington University, the task force published its recommendations in December 2001. An overview of our work was also published this January in the *New England Journal of Medicine*. The task force roster is contained in the final report, which is appended to this testimony, as is a copy of the summary article. We request that this material be entered into the record of this hearing. (The documentation was not available at press time, however copies are maintained in the committee files.) Among the 28 members of the AAMC Task Force on Financial Conflicts of Interest in Clinical Research are prominent representatives from the fields of academic medicine, law, industry, bioethics, patient advocacy, the media and politics.

The task force was charged with examining the appropriate limits of financial interests for faculty, students, and staff involved in the conduct of research with human participants, and whether certain types of financial interests should be prohibited. The task force considered the most effective means by which significant related financial interests in research involving human participants should be disclosed to the institution, the research participants, and to the public, and under what circumstances, if any, it is acceptable for institutions to invest in and sponsor faculty entrepreneurial activities involving human participants. For those circumstances that may be deemed acceptable, the task force proposed mechanisms to ensure that institutional oversight of faculty activities is responsible and credible.

Quoting from my summary article: The guidelines offered by the AAMC task force are based on some core principles. The first guideline makes it clear that the welfare of the patient is paramount. The second guideline addresses the circumstances under which researchers with financial conflicts might be allowed to participate in human research. The other guidelines define institutional responsibilities for the oversight and management of conflicts of interest, as well as the individual responsibilities of faculty members, staff members, and students. For example, the task

force recommends that full initial and updated reporting of any relevant activity be required. Moreover, institutional policies should be comprehensive, unambiguous, well publicized, consistently applied, and enforced by means of effective sanctions. The document states that "Transparency must be the watchword for the oversight of financial interests" and that "transparency is achieved through full and ongoing internal reporting and external disclosure." The task force recognized that some conflicts pose little threat to the physician-patient relationship and may even advance its primacy; they therefore adopted, as part of the complex definition of "significant financial interest in research," the threshold established by the Public Health Service of \$10,000 of total interest in companies related to the research in question for a conflict of interest in any given research project.

The report lists the requirements that must be met as institutions develop their own policies. For example, the key responsibilities of the committee that assesses conflicts of interest are identified. In addition, detailed guidance is provided on reporting requirements, the certification of investigators, disclosure practices, monitoring procedures, the protection of students and trainees, legal obligations, and sanctions. Advice is also provided on the implementation of such policies, including consideration of information flow, resources, written acknowledgment by those involved in clinical research that they have read and understood the policy, education and training of researchers, and accreditation of institutional research review processes.

The greatest challenge for the task force was reaching a consensus on the best way to ensure that the welfare of the patient remains the top priority. One sentence in the first guideline deserves further discussion; it states that, "institutional policies should establish the rebuttable presumption that an individual who holds a significant financial interest in research involving human subjects may not conduct such research." Some members of the task force and some research organizations, such as the American Society of Gene Therapy, believe that any financial conflict should preclude involvement in such research. The privilege of conducting research involving human subjects in cases which investigators have substantial financial conflicts of interest should be restricted to instances in which there are compelling reasons for an exception to be made. The AAMC task force recommended that it should be the responsibility of the researcher who has such a conflict to persuade an institutional committee that it is in the best interest of the subjects to allow the investigator to have direct involvement in the research.

Addressing investigator conflicts of interests is only part of the challenge. It is also necessary to address the management of institutional conflicts of interest. The AAMC's institutional conflict of interest task force is confronting this issue. The task force's complete report will provide detailed guidelines for the recognition and management of all institutional conflicts of interest.

The AAMC respectfully urges the subcommittee to afford academic medicine the opportunity to demonstrate that we can—and will—take the actions necessary to sustain the public trust in our institutions, our investigators, and the integrity of biomedical research, while continuing to play a seminal role in translating the remarkable fruits of the "Golden Age of Biology" into public benefit.

To conclude, the AAMC and its members are firmly committed to the protection of the rights and welfare of every individual who elects to participate in human research, and we look forward to continue working with the members of this subcommittee to achieve this goal.

PREPARED STATEMENT OF VIRGINIA A. SHARPE, PH.D.

I am Virginia Ashby Sharpe, Ph.D., Director of the Integrity in Science Project at the Center for Science in the Public Interest. Before coming to the Center for Science in the Public Interest, I was the Deputy Director of the Hastings Center, where my research focused on issues related to ethics and adverse medical events. The Integrity in Science project addresses the role that corporate interests play in scientific research, oversight, and science-based policy and advocates for full disclosure of funding sources by individuals and governmental and non-governmental organizations that conduct, regulate, or provide oversight of scientific investigation or promote specific scientific findings.

As you know, over the last 3 decades, a number of factors have spurred the commercialization of science in the United States and around the world. The genomics revolution, judicial decisions supporting patent protection for bioengineered molecules, laws strengthening intellectual property rights both in the United States and in the context of international trade, and the 1980 Bayh-Dole Act authorizing licensing and patenting of results from federally-sponsored research have created new in-

centives for clinicians, academic institutions, and researchers to join forces with for-profit industry in an unprecedented array of entrepreneurial activities.

At the same time, companies seeking to expand their market share in biomedicine, biotechnology, and other fields provide clinicians, scientists, and academic institutions with research support, consultancies, honoraria, royalty arrangements, all-expenses-paid conferences, and other gifts. Infusions of corporate money to resource-constrained public universities may be seen by legislators as a welcome alternative to the expenditure of limited State funds.

The upshot of these trends for human subjects research is that 70 percent of funding for clinical drug trials now comes from industry, and a significant number of those trials are conducted by for-profit contract institutions and private office-based physicians who operate outside the context and oversight of academic research institutions. Office-based physicians are paid to recruit patient-subjects into these drug trials and are financially rewarded if they succeed in keeping patient-subjects in a study to its conclusion.

The oversight of human subjects research within academic institutions has also increasingly come under scrutiny. Because institutional IRB membership is largely voluntary, members may have neither the time nor the commitment to pursue rigorous review of protocols. Likewise, if only those who have an incentive to move research forward at an institution volunteer for this task, there may be inappropriate incentives and quid pro quos built into the oversight process. In addition, academic institutions have increasingly come under scrutiny as they begin to have ownership stakes in new drugs and biologics whose investigational protocols are reviewed by their own institutional review boards.

Although many have cheered these partnerships between industry and clinicians, researchers, hospitals, and academic medical centers, it is also generally acknowledged that they introduce potentially biasing financial incentives into the decision-making of precisely those individuals and institutions who are charged with maintaining the integrity of science and the protection of human subjects.

We believe that legislation to strengthen human research protections should:

1. Apply protections in the "Common Rule" uniformly to all research on humans regardless of setting or funding source.
2. Enhance regulatory oversight of human subjects research by creating an independent body outside of existing Federal agencies.
3. Mandate accreditation of institutional and non-institutional review boards.
4. Mandate training for institutional and non-institutional review board members.
5. Mandate comprehensive information collection by oversight bodies of financial and other relevant conflicts-of-interest or perceived conflicts-of-interest of individual investigators and research institutions engaged in human research.
6. Mandate full disclosure to research subjects and the public of financial and other relevant conflicts-of-interest or perceived conflicts-of-interest of individual investigators, research institutions, and oversight bodies.

Because the term "disclosure" can be used ambiguously, any new legislation should clearly distinguish between "information collection" and "disclosure." Information collection should refer to the required provision of information by an individual to an oversight authority, such as a university conflict-of-interest committee, a review board, or Government agency. "Disclosure," on the other hand, should refer to the subsequent provision of that information by the oversight body to research subjects (or valid proxies) and the public. We believe that, in the context of human subject protection, it is misleading to state that a researcher or institution has "disclosed" information if that information never reaches the research subject (or valid proxy) and the public. Because financial and other conflicts-of-interest may place subjects at risk, they are entitled to information about such conflicts as part of the informed consent process.

The underlying assumption that information collection by an oversight body is an adequate safeguard against inappropriate conflicts-of-interest is that the oversight body can ensure that financial and other factors have not unduly influenced or compromised the reported activity. However, as is attested by the American Association of Medical Colleges' efforts to address institutional conflicts-of-interest and the General Accounting Office recommendations regarding the risks of institutional conflicts,⁵ there is widespread acknowledgement that institutional bodies are doing an inadequate job, in part, because they also may have significant conflicts-of-interest that compromise their ability to provide independent oversight.

When a hospital has an equity stake in a company whose product is being proposed for clinical trial to the institution's IRB, how can independent oversight be

⁵ General Accounting Office. "HHS Direction Needed to Address Financial Conflicts of Interest." GAO-02-89. November 2001. See <http://www.gao.gov/new.items/d0289.pdf>.

assured? When a university ostensibly dedicated to academic freedom stands to lose a major company gift if one of its researchers is critical of the company's products, how can the university be trusted not to silence the researcher? This persistent problem is summed up in the phrase: "Who watches the watchers?"

The Integrity in Science project believes that in a democracy, transparency through public disclosure and disclosure to research subjects is an essential minimum requirement for managing conflicts-of-interest and curbing abuses in the conduct and oversight of human subjects research. We believe that researchers, research institutions, and oversight bodies are accountable ultimately to those placed at specific risk either as research subjects in the service of science or as consumers through exposure to the drugs and devices marketed on the basis of research.

Accreditation guidelines for human subjects research review boards will undoubtedly require that boards have substantive conflict-of-interest statements and conflict management strategies, such as firewalls, threshold amounts of financial support, and recusal. We believe that the credibility and effectiveness of those substantive standards will depend on the transparency with which they are implemented. In other words, the legitimacy of substantive conflict management strategies will, at minimum, depend on disclosure of relevant financial and other conflicts-of-interest to subjects and the public.

Thus, we urge you to include mandatory disclosure of financial and other conflicts of interest in any new legislation.

Endnotes:

¹ *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

² The Patent and Trademark Act Amendments of 1980. Pub. L. No. 96-517, 94 Stat. 3019 (codified at 35 U.S.C. §§ 200-11 (1982)).

³ T. Bodenheimer, "Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry," *N. Engl. J. Med.* 2000 May 18; 342(20):1539-44.

⁴ AAMC Taskforce on Financial Conflicts of Interest in Clinical Research. "Protecting Subjects, Preserving Trust, Promoting Progress." (December 2001). See <http://www.aumc.org/members/coiff/chartercharge.htm> for forthcoming reports.

POLICY STATEMENT OF THE ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Chairman Kennedy, Senator Frist, members of the subcommittee: The Association of Clinical Research Organizations (ACRO) applauds the subcommittee for today's examination of the protections afforded to human participants in biomedical research. We believe strongly that the public must be fully confident that researchers place the well-being of human volunteers first and foremost in all clinical trials research, and that Federal regulators have available the tools to provide a high level of oversight to the system of research that has powered the development of the most advanced health care system in the world.

The members of ACRO—Covance Inc., Kendle International Inc., PAREXEL International Corp., Pharmaceutical Product Development, Inc. (PPD) and Quintiles Transnational Corp.—assist pharmaceutical, biotechnology and medical device companies with the conduct of thousands of clinical trials every year. We provide a wide range of research services, including consultation in study design, facilitation of the recruitment of investigators and study patients, assurance of the protection of patients, assurance of the integrity of the research data and the data analysis to maximize the quality of the research, and guidance through a very complex regulatory environment.

Whether providing limited support, such as assisting with the training of research site staff, or assuming full regulatory responsibility on behalf of a sponsor for all aspects of the conduct of a clinical trial, we are committed to putting the safety of research participants first. Today, ACRO members are full partners in the drug development cycle, and we are proud to be part of the clinical research that produces new drugs, new medical devices, and new treatments that improve health and save lives.

Because an uncompromising commitment to safety and quality is the hallmark of ethical research, ACRO supports new legislation to improve the protection of human subjects. We believe that such legislation should embody three basic principles:

1. Federal oversight mechanisms should be extended to as much research that includes human subject volunteers as possible.
2. Uniform human research subject protection requirements should apply to all research subject to Federal oversight, regardless of the source of funding for the research or the site where the research is conducted.
3. The Department of Health and Human Services (HHS) should be directed to review and move to "harmonize" the human subject protection requirements of cur-

rent FDA regulations (21 CFR) and the “Common Rule” (45 CFR), with the intent of promulgating standards that combine the strengths of the two regulatory approaches and improving the protection of human research subjects.

Why Clinical Trials are Crucial to Advances in Medicine

Until the mid-20th century the practice of medicine relied largely on observation. Physicians knew what worked or didn’t work based on the experience of their own patients, and the case studies described by their colleagues. With this model of anecdotal reporting, advances in understanding and treatment were often slow and painstaking, and sometimes hampered by observations that were misleading, if not simply wrong.

In the mid- to late-1940s two British physicians designed what were perhaps the first truly randomized, controlled evaluation of competing treatments (for tuberculosis) and laid the groundwork for the single greatest advance in the science of medicine in our time: the carefully conducted clinical trial that is designed to test the safety and efficacy of new drugs and new treatments in humans.

By demonstrating the importance of studying sufficiently large groups of patients in a controlled and methodical way, and developing the rigorous scientific and statistical methods necessary to obtain reliable and reproducible results, the clinical trial led directly to the concept of “evidence-based” medicine. More importantly, the widespread adoption of the clinical trial led to spectacular advances in lifespan and quality of life. The advance of clinical trials made possible the confident introduction of breakthrough drugs and treatments—new medicines to lower cholesterol and reduce the risk of heart attack; increasingly effective treatments for depression and other serious mental disorders; drugs that make AIDS more and more a disease that can be managed medically over time and not inevitably a death sentence, to cite just a few examples. In addition, the evidentiary power of clinical trials has allowed an understanding of the potential complications and serious adverse events of new treatments, such as high-dose chemotherapy with autologous bone marrow transplantation, and a sound evaluation of treatment risk. It is because of clinical trials that ever-increasing numbers of cancers and other deadly diseases can be “cured” or put into remission.

It is important to note that the occurrence of a serious, avoidable injury during the course of a well-designed and well-conducted clinical trial is extremely rare. Nonetheless, we recognize that there have been well-publicized and genuinely tragic injuries and even deaths in clinical research projects in recent years, and that the current system of Federal oversight is complex and increasingly overtaxed. While there can be no doubt that clinical trials are essential to medical progress, current protections and safeguards can be strengthened and the clinical research organizations of ACRO are strongly supportive of initiatives that will improve research practice and increase public confidence, and thereby facilitate life-saving research.

The Role of the Clinical Research Organization (CRO) in Protecting Patients

In the remarks concerning the protection of human research participants to follow, ACRO encourages the subcommittee to keep in mind three characteristics of the clinical research organization:

ACRO members have a broad perspective—on clinical research, a perspective that is global in nature and interwoven into the activities of all the participants involved in clinical trials research, including—most importantly—patients. Oftentimes, we are the only entity that has an overview of all the players on the field.

The clinical research organization has a unique role—as associate, partner, intermediary, monitor, and auditor, in relation to sponsors, investigators, patients, and regulators. Our central task is to ensure compliance with regulations, regulations that embody the application of good clinical practices and ethical behavior on a global basis.

We are committed to safety and quality—because without both we would be unable to ensure the participation in research of our most crucial partners, the patients whose willingness to take part in clinical trials is essential to making new drugs and new treatments available.

In providing research services to a sponsor, ACRO may become responsible for various aspects of the conduct of the study. Indeed, pharmaceutical companies often transfer to an ACRO member some or all of the clinical trial regulatory responsibilities stipulated by the Food and Drug Administration (FDA). Thus, the clinical research organization is involved on behalf of a sponsor in how a study is conducted—but, at the same time, may have the characteristics of an institution, if by that we mean an entity that may identify clinical investigators, provide dedicated research facilities, conduct any or all phases of the research, and interact with Federal and overseas regulators. Further, the ACRO’s role as both associate and intermediary

in relation to the sponsor, the investigator, the participant, and even the regulator makes for an extremely broad view of drug development processes, including the implementation of patient protections.

In theory, the current system for both approval and oversight of clinical research depends heavily upon institutional review boards, or IRBs. In practice, however—at least for FDA-regulated research—while the IRB undertakes the determination of whether a research protocol is appropriately designed and broadly meets a risk-benefit analysis, when the study is actually conducted it falls to sponsors and their CRO partners to provide specific individual investigator and patient-by-patient oversight: to assess the planned and actual recruitment of participants, the execution of informed consent, the collection and safeguarding of data, the reporting of adverse events and the use of data and safety monitoring boards (DSMBs), deviations from and changes to study protocols, and the like. In particular, the role of the study monitor—a research professional who is employed by the sponsor or CRO to monitor the actual conduct of the study, and who has an “on the ground” presence that is not within the scope of an IRB—is critical to the protection of clinical trial volunteers and to the integrity of the research data.

In practical terms, many of the services that a CRO furnishes to a sponsor have a direct bearing on the protection of clinical trial participants. For instance, we may provide: access to a database of well-trained, experienced investigators, especially those who provide clinical care to the appropriate patient population; experience with multi-center protocols, and international studies; trained research coordinators and research monitors; central laboratory and data management capacities; and central quality assurance functions.

All of which put us squarely on the line when it comes to protecting patient safety.

It is important to note that the CRO’s function is to ensure the quality of the research effort, not the result of any particular study. Our “bias,” if we call it that, is to facilitate quality research in the timeliest manner possible—and speed combined with accuracy can simply never be gained by cutting corners or skimping on patient protections. In short, the integrated role of the CRO provides a unique perspective on the task of overseeing the conduct of research, and the protection of human subjects, as the CRO acts on behalf of—but is also independent of—the sponsor; and in addition acts as a resource for—but, at the same time, monitor of—the investigator and site staff.

Because the large majority of our work relates to the development of drugs or devices regulated by the FDA, CROs are highly experienced with a strict regulatory approach to the protection of human subjects. We believe that with the current good clinical practices (GCP) guidelines and standards, the FDA provides excellent guidance for meeting the patient protections required in regulation. Similarly, the standards of the International Conference on Harmonization (ICH) and the Council for International Organizations of Medical Sciences (CIOMS) guide us in the conduct of international trials. In every trial the question for us is: do we do what the regulations call for, and can we prove that with appropriate documentation? This regulatory approach can be contrasted with that of the Common Rule, which utilizes a paradigm based on assurances, where the question is: has the responsible party assured that it can, and will, observe the relevant requirements?

Now some have argued that the weakness of the regulatory model is that its oversight relies on after-the-fact review of documentation rather than ongoing monitoring. But the answer to that problem, in our view, is not to ask IRBs to do something they simply are not designed or equipped to do—particularly since CRO coordinators, monitors, data managers, biostatisticians and others are, in fact, coordinating the performance and monitoring the actual conduct of the research in real-time today. Instead, perhaps we need a combined approach, an approach to oversight that integrates the “assurance” and “regulatory compliance” models in a way that both trusts and verifies—because, in ACRO’s view the highest ethical and scientific aspirations mean little unless we actually protect our patients and we can prove it.

Improving Current Protections

The current system of human research participant protections is neither as uncontrolled and inadequate as some seem to think, nor as over-regulated and stymied by bureaucracy as some protest. It is a system that relies on the training and ethics of physicians and many others to conduct scientifically rigorous, meaningful and useful research. In truth, it is largely successful—enabling spectacular advances in drug treatments and other therapeutic interventions, and in overwhelming measure it wins a vote of confidence from its most important constituents: the human research volunteers themselves. At the same time, however, we recognize that existing regulations are inconsistent, overlapping and do not cover all human subject re-

search—and that patients, investigators, IRBs, and all research participants would be better served by a set of regulations that could be uniformly and consistently applied.

In our experience, current FDA and international regulations provide strong protections for volunteers enrolled in clinical trials intended to test new drugs, new devices, and new treatments. This regulatory framework, however, does not extend to many studies, including much Government-funded research and an unknown amount of private research that is not intended for submission to the FDA, and we applaud the subcommittee's examination today of gaps and weaknesses in the oversight system.

Again, ACRO believes that legislation intended to improve the protection of human subjects should embody three basic principles:

1. Federal oversight mechanisms should be extended to as much research that includes human subject volunteers as possible.

2. Uniform human research subject protection requirements should apply to all research subject to Federal oversight, regardless of the source of funding for the research or the site where the research is conducted.

3. The Department of Health and Human Services (HHS) should be directed to review and move to “harmonize” the human subject protection requirements of current FDA regulations (21 CFR) and the “Common Rule” (45 CFR), with the intent of promulgating standards that combine the strengths of the two regulatory approaches and the goal of improving the protection of human research subjects.

Specific issues relevant to the protection of human subjects that should be examined by the Secretary of HHS include initiatives to help: clarify and improve the informed consent process; strengthen and provide additional support to the IRB system; clarify and improve the processes for evaluating and, when necessary, disclosing potential financial conflicts of investigators, institutions and IRBs that may affect the conduct of research; assure the familiarity of all parties involved with clinical research with the scientific and ethical principles that underlie the protection of human subjects; and, in general, to strengthen consistent regulatory compliance, and the conduct of highest quality research.

For our part, ACRO does not intend to wait for Congressional action but has already begun to consider both smaller and larger scale initiatives aimed at improving still further a record of safety and quality of which we are very proud. For instance, many CROs strongly encourage the certification of study coordinators (CRCs) and study monitors (CRAs) as a basic indicator of research and regulatory knowledge and experience. Similarly, we have strongly supported investigator participation in education and training opportunities offered by the Office for Human Research Protections (OHRP), the FDA and the NIH. And we have begun to look at a number of other issues that may impact the conduct of clinical research and the protection of human subjects, such as: the recruitment and training of investigators, with special attention to first-time investigators; “best practices” for patient enrollment and the execution of informed consent; the use of voluntary certifications for investigators and other personnel; mitigating negative effects of financial conflicts of interest, and examining policies regarding the use of financial incentives for both patients and investigators; and participation in self-regulatory initiatives, such as taking part in the educational and quality improvement initiatives undertaken by the OHRP.

Conclusion

The Association of Clinical Research Organizations (ACRO) thanks Chairman Kennedy, Senator Frist and the members of the subcommittee for today's hearing. Your recognition of the need to improve the safety of those who volunteer to participate in clinical research and, at the same time, to increase public confidence in the system of medical research that produces new drugs and new treatments to improve health and save lives every day is vitally important to what Senator Kennedy has called “the century of the life sciences.” ACRO appreciates the opportunity to share our views with the subcommittee, and our members stand ready to work closely with you on legislation of great importance to all Americans.

The hearing stands in recess.

[Whereupon, at 11:35 a.m., the hearing was adjourned.]